



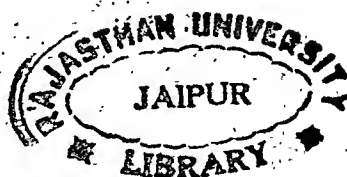
# ANNALS *of* ALLERGY

*Published by the  
American College of Allergists*



VOLUME 5

January through December, 1947



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# ANNALS of ALLERGY

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# ANNALS *of* ALLERGY

*Published by the  
American College of Allergists*

Volume 5

January-February, 1947

Number 1

## BACTERIAL ALLERGY

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THERE appears to be much confusion as to the implications of the term "bacterial allergy." Some use it only in connection with the relationship of bacteria to that group of allergic conditions designated by Coca as atopy. Others associate the term only with those types of hypersensitiveness that result from bacterial infection. Still others use it in the generic sense to include all types of hypersensitive reactions that may develop when the tissues are brought in contact with bacteria or their products or extracts of the organisms. It is in this generic sense that the term bacterial allergy will be employed in this discussion. The types of hypersensitiveness to be treated have been designated: (1) bacterial anaphylaxis (including toxin hypersensitiveness), (2) bacterial atopy, (3) tuberculin-type hypersensitiveness, (4) the Shwartzman reaction, and (5) bacterial heterophile toxicity.

### BACTERIAL ANAPHYLAXIS

Any substance that has been proved to be antigenic, by its ability to stimulate the production of antibodies will, when injected into an animal, cause it to develop, after a suitable period of incubation, a state of hypersensitiveness which is known as anaphylaxis. An injection of the same antigen any time following the termination of the incubation period (shocking dose) will precipitate the train of symptoms which characterizes anaphylactic shock.

These symptoms vary according to the species of animal, and the method by which the antigen is administered, but not with the type of antigen. In all species of animals, however, there is a subnormal temperature and a fall in blood pressure, and the most striking symptoms are

Lecture delivered at the Graduate Instructional Course of the American College of Allergists, Jefferson Medical College, Philadelphia, Pa., November, 1946.

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JANUARY-FEBRUARY, 1947

due to the effects upon the smooth muscles. In guinea pigs there is extreme respiratory embarrassment due to the contraction of the abundant supply of smooth muscles in the bronchioles. The animals develop nasal and bronchial changes similar to those seen in human beings with asthma and vasomotor rhinitis. Death is due to suffocation. Rabbits do not show marked symptoms, as a rule, except those of collapse. Death is due to heart failure. The muscles of the pulmonary arteries cause constriction of these vessels, with blocking of the pulmonary circulation. The right side of the heart is dilated by the back pressure. The dog shows symptoms of restlessness, diarrhea and vomiting, followed by epileptiform seizures, coma and death. The liver and intestines are congested. Cattle show uneasiness, labored breathing, edematous swellings around the eyes, udder, anus, and vulva, and diarrhea. They seldom, if ever, die as the result of the shock. Monkeys are not easily sensitized, which suggests that man probably is not easily rendered anaphylactic; as is borne out by clinical experience. Indeed, it is doubtful if anaphylaxis, as it occurs in animals, ever occurs in man. Those crises in man that are similar in clinical appearance to anaphylactic shock may be the result of a somewhat different mechanism. While different animal species react with entirely different trains of symptoms, for each species the symptoms of anaphylactic shock are the same, no matter what antigen is involved.

The anaphylactic state may be passively transmitted to normal animals by transfusing them with blood or serum from a hypersensitive animal. An animal thus passively sensitized will give the anaphylactic reactions if, a few hours after the transfusion, it is given an injection of the antigen to which the donating animal was sensitized. This indicates that an anaphylactic antibody is present in the blood of the actively sensitized animal.

Another method of recognizing the presence of the anaphylactic state is the one devised by Dale. A piece of smooth muscle such as a strip of the uterus from a sensitized virgin female guinea pig is immersed in Ringer's solution kept at 37° C., and one end is connected with a kymograph needle. Upon the addition of a small quantity of the specific antigen to the solution, characteristic contractions of the uterus will be recorded on the kymograph drum. The sensitivity of the excised muscle reveals that the anaphylactic antibody is not confined to the blood stream, but is present in the tissues as well.

The anaphylactic reaction is specific. As in other immunological reactions, the specificity of a complex antigen, e.g., lipo-protein, is influenced by the hapten (nonprotein) portion of the antigen. Here too, the hapten alone will react with the antibodies produced by the injection of the complex antigen, but will not cause the production of antibodies. In an animal sensitized by such an antigenic complex, the hapten alone will elicit shock and the Dale reaction (smooth muscle contraction), although it cannot sensitize an animal. Thus, haptens assume the same role in anaphylaxis as they do in other immune reactions.

Animals in the anaphylactic state are also skin sensitive. An intracutaneous injection of the specific antigen is followed within a few minutes by a local reaction of edema and erythema which shortly disappears.

If repeated subcutaneous injections of antigen are given a rabbit at intervals of several days, not only will the anaphylactic state become established, but, in addition, the capacity of the tissues to react locally at any site at which the antigen is injected becomes greatly intensified. The initial reaction of edema and erythema persists and increases in size and intensity until in the course of about two days, hemorrhage and necrosis appear, with the formation of a sterile abscess at the site of injection. This is the Arthus reaction. Specific precipitin is demonstrable in the serum of the animal and the capacity to react locally in the Arthus manner is passively transferable to a normal animal by the injection of serum from the hypersensitive one.

Although the amount of antigen required to elicit the Arthus reaction is greater than that required for the usual local anaphylactic type, no amount of the antigen will produce the Arthus reaction in an animal that is only in the anaphylactic state. Some regard the Arthus reaction, therefore, as a manifestation of a higher degree of anaphylactic sensitivity.

In man an Arthus-like reaction may occur in the course of rabies vaccination. It appears in the form of indurated areas at the sites of inoculation after the sixth or seventh injection of the vaccine.

Animals that recover from an anaphylactic shock are desensitized and remain so for a considerable length of time. It is possible to forestall the development of the anaphylactic state by injecting large doses of the antigen during the later days of the incubation period, in which case desensitization occurs without the appearance of shock. Animals may also be desensitized, without the production of shock, by the administration of the antigen in multiple small-doses over a considerable period of time.

That bacteria are capable of producing anaphylaxis was first demonstrated by Rosenau and Anderson (1907) who sensitized guinea pigs with subcutaneous injections of extracts of colon, tubercle, anthrax, and typhoid bacilli. Kraus and Doerr (1908) then proved that bacterial anaphylaxis was passively transferable by showing that guinea pigs which were injected with the sera from guinea pigs that had been sensitized to typhoid and cholera organisms, respectively, became sensitized to the homologous organisms. Later, Zinsser and Parker (1917) demonstrated by the Dale test that uterine strips from young guinea pigs passively sensitized with antityphoid serum from a rabbit gave typical contractions when extracts of typhoid bacilli were added to the bath. Gay and Claypole (1914) found that typhoid immune rabbits were skin sensitive to typhoidin and that the sensitivity was passively transferable. Julianelle (1930) also showed that rabbits which received intracutaneous injections of heat-killed pneumococci became skin sensitive to pneumococ-

cus nucleoprotein, and that the sensitivity was passively transferable. The sensitivity to bacterial haptens of animals anaphylactically sensitized to bacteria was demonstrated by Enders (1929), Morris (1936) and others. Enders elicited typical anaphylactic reactions with tubercle bacillus carbohydrate in guinea pigs passively sensitized with antitubercle bacillus rabbit serum. Morris obtained anaphylactic reactions with the polysaccharide of the Friedlander bacillus in animals that were injected with a Friedlander bacillus antiserum. Morris also completely desensitized the animals with injections of the polysaccharide of the organisms. Thus, all of the analogies with nonbacterial anaphylaxis (shock, passive transfer, uterine sensitivity, skin sensitivity, sensitivity to specific haptens, and specific desensitization) have been fulfilled with bacterial materials.

Other organisms, in addition to those already referred to, whose extracts have been found to be capable of sensitizing guinea pigs are *Bacillus subtilis*, *Brucella abortus*, *Malleomyces mallei*, *Neisseria intracellularis*, *Neisseria gonorrhoeae*, *Treponema pallida*, and, incidentally, yeasts. It will be noted that among the organisms found capable of inducing anaphylactic shock are two nonpathogenic species of bacteria, one a commensal (*E. coli*) and the other a saprophyte (*B. subtilis*), as well as yeasts (also nonpathogenic).

Typical anaphylactic reactions have also been produced in guinea pigs actively sensitized with diphtheria toxin and toxoid, and in those passively sensitized with antitoxic sera derived either from guinea pigs or from human beings. To prove that the hypersensitiveness was due to the toxin itself and not to any other bacterial product in the filtrate, Neill and Fleming (1929) removed all detectable traces of other antibodies without removal of the antitoxic antibodies by absorbing diphtheria antitoxic sera with heavy suspensions of the diphtheria bacilli, and used the absorbed antisera for passive sensitization experiments. The absorption removed from the antisera all precipitins and all capacity for passive sensitization against nucleoprotein solutions. They concluded that the animals which became passively sensitized with the absorbed antiserum could have been sensitized only to the toxin in the toxic filtrate.

#### BACTERIAL ATOPY

The term atopy, introduced by Coca, differentiates those hypersensitive reactions occurring in man, in which antibody-like substances (reagins) are present but in which only local passive transfer is possible, and then only from man to man. Atopy has many of the characteristics of anaphylaxis—the dependence upon an antibody-like mediating substance (reagin); the immediate local response to intracutaneous injection of the allergen (atopen), with edema and erythema of short duration; the respiratory symptoms; the capacity for desensitization; and the passive transfer of skin sensitivity (the Prausnitz-Küstner reaction). It differs from anaphylaxis in the nature of the mediating substance, the absence of demonstrable specific precipitins, the tendency for certain tissues to be-

come sensitized, the influence of heredity, the spontaneous occurrence, the susceptibility of only the skin to passive transfer, and the absence, usually, of violent reactions and death.

The relation of bacterial infection to asthma and other manifestations of atopic hypersensitiveness in man has been the subject of much controversy. Many allergists are unwilling to accept hypersensitiveness to infecting bacteria as an explanation of such conditions as asthma and hay fever because the skin reactions obtained with bacterial products are of the delayed and inflammatory nature instead of the immediate urticarial type obtained with simple protein extracts. They also point to the fact that treatment with vaccines rarely produces general reactions with urticaria and coryza. Others, on the other hand, hold that when the patient has one or two attacks of asthma during the year, although there has been no change in his environment, occupation and diet, and when the attacks are definitely associated with an acute respiratory infection, it is reasonable to make the diagnosis of "bacterial asthma" and to assume that the bronchial spasm is dependent upon the infection. They believe that a hypersensitiveness to the infecting bacteria and their products, alone and without the intervention of other foreign proteins, may result in allergic symptoms; that respiratory infections alone can cause asthma; and that acute and chronic infections can produce urticaria.

There are other ways in which bacterial infections can influence allergy.

1. The resistance of the body to the entrance of foreign substances is lowered during infections. Hence it is not unusual for a hypersensitive reaction to originate in association with an infection.

2. In patients who are already hypersensitive, mild infections, such as colds, can precipitate the manifestations of allergy, by lowering the threshold so as to make a slight contact with foreign substances adequate to produce symptoms.

3. In severe febrile infections, the allergic symptoms will disappear due, probably, to a nonspecific effect.

4. Infections may complicate an original simple condition.

The role of nonpathogenic bacteria in atopy is not too clear. Considering the ubiquity of these microorganisms, the constant exposure of the skin and the mucus membranes to them, and the minuteness of the dose of allergen that will elicit such allergic reactions as hay fever, it would not appear unreasonable to suspect them of being associated with atopic conditions. Closely related microorganisms, the molds, have been proved to be associated with various types of allergic conditions in man, and nonpathogenic bacteria, commensals (*E. coli*) as well as saprophytes (*B. subtilis*), are antigenic, and have been proved to be capable of inciting hypersensitiveness of the anaphylactic type when injected into guinea pigs. Weil (1946), in a recent editorial, has stated that "there is no basic reason why persons of the necessary constitutional make-up should not react



vehemently to bacterial antigens. In the case of asthma this is quite widely and naïvely accepted to be the case" although "there is no proof"—"not because there is nothing to be proved but because we really have made no systematic effort to prove or disprove." Weil has laid down the gauntlet to the bacteriologist stating, "Only by putting to use the painstaking methods of modern bacteriology, will we be able to replace notions by exact information. And this information will be necessary before we can state with any degree of confidence whether or not microbial antigens are involved in a given manifestation of allergy."

#### TUBERCULIN-TYPE HYPERSENSITIVENESS

The two types of hypersensitiveness discussed thus far may occur whether the organisms involved are pathogenic or not. A third type of reaction, because it occurs only in the infected individual, is variously referred to as bacterial hypersensitiveness, infection hypersensitiveness, infection allergy or tuberculin-type hypersensitiveness.

Of these terms, tuberculin-type hypersensitiveness has been chosen for use in this discussion because it expresses more accurately the type of reaction to be dealt with. The other types of hypersensitiveness can also occur as a result of infection, consequently the term infection hypersensitiveness or infection allergy could, with equal propriety, be applied to the other types of allergy if the offending agent happened to be of infectious origin.

When pathogenic bacteria, living or dead, or their products are introduced into the tissues, the effects produced differ in different species and with different organisms. If, for example, living organisms of the toxigenic group such as *Corynebacterium diphtheriae* or *Clostridium tetani* are introduced, infection will result. If the tissues can produce enough antitoxin to neutralize the toxin, recovery will take place and antitoxic immunity will be established. The existence of this type of immunity is detectable by skin tests such as the Shick or the Dick tests, or by the ability of the individual to withstand with impunity injections of the causative organism or its toxin. The immunity may exist for a considerable or indefinite period of time following the disappearance of the infection.

Infection with such organisms as *Mycobacterium tuberculosis*, streptococci, *Diplococcus pneumoniae* or some members of the *Enterobacteriaceae* may also result in the formation of circulating antibodies. These antibodies may be utilized to demonstrate the presence of infection by immunological or serological methods (complement fixation tests, agglutination tests, et cetera). In addition, however, after the infection has been established, the injection of either the organisms themselves or their products, instead of producing no reaction at all or of stimulating antibody production (as would occur upon injection into a normal control), is followed by an abnormal delayed type of reaction, usually occurring within twenty-four hours. This is typified by the reactions that are induced in the tuberculous

guinea pig upon the injection of tuberculin (tuberculo-protein). If the injection is made intracutaneously, there appears in from eight to forty-eight hours a local reaction consisting of an area of edema and erythema, 1 to 2 cm. in diameter, with a central area of necrosis, the intensity of the reaction varying with the dose and potency of the tuberculin, and the hypersensitive state of the animal. The reaction gradually subsides, and fades after seventy-two hours. Microscopic examination of an excised reacting area reveals capillary dilatation, general congestion, some fibrin, and a large number of polymorphonuclear and mononuclear leucocytes.

The subcutaneous injection of tuberculin into a tuberculous animal is followed by three types of reaction: a local reaction at the site of injection, characterized by the classical symptoms of inflammation; a focal reaction about the tuberculous process, the severity depending upon the dose of tuberculin injected, but usually consisting of edema, congestion and hemorrhage; and a general reaction marked by symptoms of fever, chills, rapid pulse, malaise, anorexia, and prostration, and terminating in death.

The tuberculin-type hypersensitiveness differs from bacterial anaphylaxis and from bacterial atopy in several ways.

1. When the infecting agent, or its soluble protein is injected into the skin of the sensitized body, instead of causing a prompt wheal and erythema which disappears in a few hours, as in the simple anaphylactic or atopic reaction, (or which progresses to necrosis as in the Arthus reaction), there occurs a delayed inflammatory reaction which begins to appear only after some hours, and then progresses to reach a maximum size and intensity within twenty-four to forty-eight hours, after which it slowly fades.

2. The local reaction is characterized macroscopically by erythema, and by indurated swelling that contrasts with the soft, edematous, swelling of the anaphylactic or atopic reaction. In the more intense reactions, necrosis and sloughing of the skin occur.

3. The tuberculin-type hypersensitiveness cannot be transferred to a normal individual by the injection of serum from a hypersensitive one.

4. The cells of the body with tuberculin-type hypersensitiveness which have so far been tested (spleen, blood leukocytes, bone marrow) are killed in vitro by contact with the specific bacterial protein, whereas such cells from the body with anaphylactic, Arthus, or atopic type of hypersensitiveness are not killed in vitro by contact with the specific agent.

The tuberculin-type hypersensitiveness differs from bacterial anaphylaxis also in the following respects:

1. When the antigen is injected into an animal subcutaneously or intravascularly, the animal may become severely ill, or may die; but instead of the prompt, sudden collapse that is characteristic of anaphylactic shock, the symptoms appear only after a lapse of some hours and increase gradually in intensity, and if death occurs it is usually not before eighteen

to twenty-four hours. At any site in the body at which there is a focus of infection caused by the specific microorganism, inflammation, necrosis, and hemorrhage may occur (the so-called "focal reaction").

2. Whereas almost any soluble protein will induce the anaphylactic type of hypersensitiveness, for the establishment of the tuberculin type, parenteral contact with living or dead bacteria or filterable viruses is ordinarily necessary. The soluble proteins of the bacteria will readily elicit the tuberculin-type reaction once this form of hypersensitiveness has been established.

3. Neither carbohydrates nor lipids (haptens) have been shown to be capable of eliciting the tuberculin-type reaction in the hypersensitive body.

4. In contrast to anaphylactic hypersensitiveness, in which sensitivity appears to be limited to involuntary muscle, vascular endothelium and, possibly, certain glandular cells, there is a more widespread sensitivity of the body cells in tuberculin-type hypersensitiveness.

5. The sensitivity of excised smooth muscle (the Dale reaction) is not demonstrable in tuberculin-type hypersensitiveness.

With regard to the mechanism of the tuberculin-type hypersensitiveness, there is ample evidence that the sensitizing antigen is derived from the bacterial cells and is highly specific, that toxins or other unstable bacterial antigens are not involved, and that inflammatory cellular reactions are essential in its development. No antibodies or antibody-like substances akin to reagin that would account for the hypersensitiveness have been demonstrated in individuals with the tuberculin type. Nevertheless, Rich (1944) is strongly of the opinion that antibodies are produced and are involved in the mechanism of this type of hypersensitiveness. He reasons that the fact that the antibody is not present in the blood in amounts sufficient to permit passive transfer is not convincing proof that tuberculin hypersensitiveness is not determined by antibody, for, he points out, even in anaphylactic hypersensitivity, in which sensitizing antibody is readily demonstrable in the serum, the circulating increment of antibody is an excess which is entirely unnecessary for the hypersensitive reaction. Even in anaphylaxis the effective antibody is that portion which is intimately associated with the cells. If hypersensitive tissues of the anaphylactic animal (uterine muscle) are perfused until the circulating fluid contains no more detectable antibody, they still react anaphylactically *in vitro* on contact with the antigen. Furthermore, anaphylactic hypersensitivity persists in the intact body after the animal's blood has been replaced by normal blood.

It is possible, therefore, that the conditions governing the development of tuberculin-type hypersensitiveness may be such that a sufficient amount of antibody is produced to sensitize the tissues, but not enough to accumulate in the circulation in an excess amount sufficient to detect with any regularity in passive transfers. Attempts have been made to extract sensitizing antibody from the tissues of the tuberculous body, but the

results have been irregular and far from satisfying, although some investigators, including Rich, have reported that they have had rare, suggestively successful results. Recently, Chase (1945) succeeded in producing, in normal guinea pigs, a transient cutaneous hypersensitiveness to tuberculin that exhibited the essential features of the typical tuberculin reaction, by injecting them with cells secured from the peritoneal exudates, or spleens; or lymph nodes of tuberculin sensitive guinea pigs.

In further support of the antibody concept, Rich points to five additional observations, as follows:

1. The high degree of the specificity of the hypersensitiveness. Tuberculin-type hypersensitiveness may become established during infection with most if not all microorganisms, and when it is established, the body will react characteristically and in a highly specific way to the protein of the particular infecting microorganism.

2. The anamnestic reaction. When a specific antibody has once been produced as a result of contact of the tissues with a foreign antigen, the amount of antibody demonstrable in the circulation gradually decreases with the passing of time if there is no further contact with the same antigen, until, at length, none at all can be detected. If now the antigen enters the tissues again, antibody will reappear in the circulation, and will reach a given level in a much shorter time than was required following the first contact with the antigen. It is significant, therefore, that this anamnestic effect that is so characteristic of antibody development in general, is also a characteristic of tuberculin-type hypersensitivity. Following a well-resisted tuberculous infection in animals and in man, hypersensitivity often wanes, and after several years it may decline to so low a level that large doses of tuberculin will fail to produce a reaction. If, now, re-infection occurs, hypersensitivity will reappear in a shorter time than was required for its establishment following the first infection.

3. The condition present in the white rat. This animal is a poor antibody producer and, similarly, exhibits little tendency to develop the anaphylactic type of hypersensitiveness which is dependent upon antibody. The rat displays the same refractoriness to the development of tuberculin-type hypersensitiveness following infection with the tubercle bacillus as it does to the development of anaphylaxis.

4. The phenomenon of specific desensitization. As in anaphylaxis, so too in tuberculin-type hypersensitiveness, the hypersensitiveness can be depressed or abolished by desensitization; and by the same desensitization procedures (injection of a single large dose, or of repeated, increasing doses of the specific protein).

5. Enhancement of hypersensitiveness. A procedure (suspension of the bacilli in paraffin oil before injection) that is known to enhance markedly the production of antibodies to the tubercle bacillus, also enhances markedly the degree of hypersensitivity.

Rich concludes that it seems highly probable that tuberculin-type hypersensitiveness is dependent upon antibody, but that in contrast to other types practically all of the antibody is closely associated with the cells, and too little excess antibody accumulates in the circulation to permit passive transfer. He concedes, however, that it is possible that an acquired capacity to react specifically to a foreign protein may be effected through some as yet undefined and undiscovered mechanism that is entirely independent of antibody.

In a number of infectious diseases, the development of the tuberculin-type hypersensitiveness is utilized in a practical way for diagnostic purposes. For example, to detect the presence of tuberculous infection, individuals may be tested for hypersensitiveness to tuberculin. The testing may be done by von Pirquet's cutaneous method, in which the tuberculin is rubbed on to the scarified skin; Moro's percutaneous method, in which the tuberculin is incorporated in an ointment and rubbed into the skin; Mantoux's method, in which the tuberculin is injected intracutaneously; Calmette's ophthalmic method, in which the tuberculin is dropped into the conjunctiva; Koch's original method, in which the tuberculin is injected subcutaneously; or Vollmer and Goldberger's patch test, in which a thin filter paper, impregnated with tuberculin and then dried, is applied to the skin. In all of the skin tests, a positive reaction consists in the appearance, after forty-eight hours, of edema and redness of varying degrees. In the ophthalmic test, which is used only in lower animals, a positive reaction consists of a conjunctivitis during the course of which pus is formed and appears at the inner canthus. In the subcutaneous test, a positive reaction consists of a rise in temperature of at least 2° F., which appears some time between the eighth and eighteenth hours following the injection and subsides within twenty-four hours. This test has not been used in human beings, and even in the lower animals it has been largely replaced by the intradermal tests.

Other infectious diseases in which the test for tuberculin-type hypersensitiveness has been employed for diagnostic purposes are: glanders of horses, using mallein; contagious abortion of cattle, using abortin; brucellosis, using brucellin; para-tuberculosis of cattle, using johnin; and syphilis, using luetin. Intradermal tests have also been described for gonococcal and meningococcal infections, typhoid fever, tularemia, rhinoscleroma, soft chancre, actinomycosis, typhus fever, and pullorum disease in chickens, as well as for certain parasitic infections.

In virus diseases, a similar type of hypersensitiveness has been observed. The characteristic response to reinoculation with vaccinia virus is one of the classical examples. If a person who has been successfully vaccinated is again injected with the vaccine during the period of decreasing immunity, but before he has again become fully susceptible, the papules appear earlier (sometimes within twenty-four hours), and vesiculation and pustulation, when they occur, appear much earlier than after pri-

mary vaccination. Very frequently, however, the reaction ceases at the papular stage, and even this may be so transitory as to be missed unless daily examinations are made. There is usually much less induration around the papules or vesicles after a secondary than after a primary vaccination, and the constitutional symptoms are milder. In other words, there is the typical hypersensitiveness combination of accelerated response with localization of infection. Vaccinia virus killed by heating to high temperatures is capable of producing the characteristic early reaction with papule formation in persons previously vaccinated; while it has no effect in unvaccinated persons, nor does it produce an active immunity. Desensitization of individuals who exhibit the hypersensitiveness to vaccinal protein may be accomplished by repeated injections of killed virus.

Among the theories that have been advanced to explain the etiology of postvaccinal encephalitis is the hypersensitiveness one. It is thought that hypersensitiveness is the primary factor in causing the thrombosis which produces the characteristic histological picture of demyelination in this condition.

On the experimental side, Force and Beckwith (1915) introduced a laboratory test for the diagnosis of smallpox, which depended upon hypersensitiveness reactions. They sensitized rabbits by inoculating them with vaccinia and later inoculated them with the contents of smallpox vesicles. The animals developed a severe intradermal reaction in twenty-four to forty-eight hours. Blaxall (1923) obtained similar results, even with boiled variolar antigen and Thompson (1930) found that the hypersensitiveness could be passively transferred by injection of serum. Dienes and Naterman (1937) found that the skin reactions also developed in guinea pigs on revaccination. The reactions were of the "delayed type," and were characterized, microscopically, by infiltration with large mononuclear leucocytes.

Patients with lymphogranuloma inguinale, a venereal disease caused by a virus, are hypersensitive to sterilized pus from the bubos, and develop the usual skin reaction within twenty-four hours, when the material is injected intradermally. This is the Frei diagnostic test. The skin hypersensitiveness develops quite early in the disease and persists for a long period after recovery. Upon intravenous injection, the antigen gives rise to a febrile response. Antigens have also been prepared from infected mouse brain and, more recently, from infected chick embryo. The latter is said to give rise to fewer nonspecific reactions than the mouse brain antigen. Melczer and Sipos (1938) have reported that the hypersensitiveness to the Frei antigen can be transmitted by injections of blood serum, and be demonstrated by the Prausnitz-Kustner technique.

In experimental poliomyelitis, Brebner (1931-2) found that if the virus was injected into the spleen of immune monkeys (either by recovery from infection or by vaccination) sudden death occurred. Death did not result unless about seven weeks had elapsed since the beginning of

immunization, or the onset of the paralytic attack. That such a finding might be due to a hypersensitive reaction was suggested by the post-mortem appearance of hemorrhages in the mucous membranes, necrosis of the liver lobules, and hemorrhages in the medulla. Jungeblut (1931) has also indicated that the altered response of a prolonged febrile disturbance, which develops three to four days after intracerebral injection of virus into monkeys which had been injected parenterally on a number of occasions, is suggestive of a hypersensitive phenomenon.

Another virus disease in which the hypersensitive state has been observed is Virus III infection in rabbits. Andrewes (1928) has reported that rabbits which had been solidly immunized showed a relatively small local lesion when inoculated in the testes, but no nuclear inclusions were present in these lesions. Partially immunized rabbits developed more pronounced testicular lesions, as judged histologically, than did either normal or solidly immunized animals. The lesions, however, unlike those produced in normal rabbits, were usually free from nuclear inclusion bodies.

It is highly probable that detailed studies would reveal the presence of infection hypersensitiveness in other virus infections.

Incidentally, in recent years, another problem in allergy has arisen as a result of the use of virus or rickettsial vaccines prepared by growing the organisms on egg yolk sacs or chick embryos. Individuals who are sensitive to egg or chicken may develop allergic manifestations if they are given vaccines prepared in this manner.

The tuberculin-type hypersensitiveness has been suggested as a possible explanation of some features of rheumatic fever, particularly the joint lesions and the fever, and possibly also the typical Aschoff modules. An attack of streptococcic sore throat often precedes the onset of rheumatic fever. Rheumatic patients are not infrequently hypersensitive to streptococci, and the injection of small doses of dead streptococci will produce in them far more severe reactions than in normal subjects. Swift and his collaborators (1928) induced hypersensitiveness to *Streptococcus viridans* in rabbits which, on subsequent injection of the organisms reacted with extreme edema. Zinsser and his associates (1939) have summarized the premises upon which the hypersensitive view of rheumatism is based as follows:

"1. In acute and subacute rheumatic conditions, the joint fluids are usually sterile, though signs of inflammation are present.

"2. The organisms isolated from rheumatic cases are not bacteriologically or serologically identical.

"3. *Streptococcus foci* are found in many rheumatic cases.

"4. Joint lesions can be produced in animals with products of these organisms, and such joint hypersusceptibility can be shown to some extent to be parallel with skin allergy."

In scarlet fever, the tuberculin-type hypersensitiveness is also thought to play an important role. In this disease, the evidences of septicemia are due to the invasion by the streptococci themselves, whereas the characteristic symptoms are due to the effects of the soluble exotoxin. This toxin is present in the broth filtrate of cultures of the organism and differs from other exotoxins by not being affected by age. It is toxic only for man; animals and young infants are not affected. Many believe, therefore, that the rash and clinical symptoms may be due to an acquired hypersensitiveness to the products of the organism and that the supposed exotoxin is in reality a nontoxic antigen. Infants at birth are negative to intracutaneous injections of the scarlatinal filtrates and their blood sera possess no neutralizing power. If they later become infected with streptococci, they become sensitized so that a subsequent infection with the same organism gives rise to an allergic reaction which is manifested by the toxic syndrome of scarlet fever.

Infection with pneumococci, or vaccination with dead pneumococci, produces cutaneous hypersensitiveness of the tuberculin type. Animals so sensitized by the intact bacteria give delayed tuberculin-type skin reactions to the injection of intact pneumococci or of the soluble protein. If, on the other hand, the soluble pneumococcal protein is injected repeatedly into a normal animal, a state of hypersensitiveness is established in which the cutaneous reaction produced by the injection of the protein resembles the Arthus reaction, and this hypersensitiveness is passively transferable.

Among the more recent reports of diseases in which tuberculin-type hypersensitiveness is considered to be involved are: (1) different ocular affections, particularly phlyctenular conjunctivitis, attributed by Ré (1944) to hypersensitive reactions to tubercle proteins; (2) erythema nodosum, considered by Sigalov (1944) as usually the expression of early hypersensitiveness to tubercle bacilli, with a local exacerbation of the tuberculous process either preceding or accompanying the eruption, and by Dementiev (1944) as a definite hypersensitive syndrome caused by various diseases but in the majority of his cases by tuberculosis, and (3) periarteritis nodosa, regarded by Wilson and Alexander (1945) as associated in some cases with hypersensitiveness to bacteria.

The popularity of penicillin as a therapeutic agent has given rise to another problem in which the tuberculin-type hypersensitiveness is involved. Rostenberg and Welch (1945), in a study of the types of hypersensitiveness induced by penicillin, found that the incidence of the tuberculin type to crystalline penicillin sodium in a group of 144 persons was 5.5 per cent. None had had prior contact with penicillin. Cormia et al (1945), in a study of 2,000 persons who received penicillin, reported that 0.5 per cent showed reactions so severe that treatment had to be stopped. They suggest that a previous fungus disease may enhance the development



of reactiveness to penicillin, and state that testing with penicillin has been of limited value as an aid in diagnosis and a guide for further treatment.

#### THE SHWARTZMAN REACTION

Shwartzman (1937) found that if bacterial filtrates, e.g., typhoid, are injected into the skin of normal rabbits and, twelve to twenty-four hours later, the same or different bacterial filtrates are injected intravenously, a severe reaction occurs at the site of the original skin (preparatory) injection. The reaction develops in about four hours after the intravenous (provocative) injection and consists of hemorrhage and necrosis. The skin loses its capacity to react in about forty-eight hours after the preparatory skin injection. A second injection directly into the prepared skin site fails to produce the reaction; the second injection must be made intravascularly. The reaction is not specific, since the filtrate of an entirely different species of bacterium than that used for the preparatory injection may be used for the intravenous injection, and it is not passively transferable. Nonbacterial substances such as egg albumen or horse serum have failed to reproduce the phenomenon. The bacterial filtrates are neutralized by specific immune sera.

The mechanism of the reaction has not been determined. Shwartzman states that it is not a mere trauma, it is not due to the local blockade of reticuloendothelial cells nor merely to increased permeability of the capillaries nor to inflammation, and that it is entirely unrelated to anaphylaxis. He does not believe that the reaction is one of anaphylactic shock because (1) it requires an incubation period of about twelve hours and cannot be elicited after forty-eight hours, while the incubation period for anaphylaxis is about ten days and sensitivity lasts for months or years; (2) there is no specific relationship between the preparatory and provocative factors, as there is in anaphylaxis; (3) it can only be produced by certain bacterial filtrates, while any antigenic substance can elicit anaphylaxis; (4) it cannot be passively transferred while anaphylaxis can; (5) both the preparatory and provocative factors are neutralizable by immune sera, and (6) there is no specific desensitization as there is in anaphylaxis. Shwartzman concludes that his phenomenon deals with a hitherto unrecognized functional disturbance in the susceptibility of the animal tissue which is elicited by certain bacterial active principles and that it displays a mechanism whereby injury may be produced through the synergistic effect of bacteria and their products and also through the concerted effect of bacteria, their products and nonrelated anaphylactic processes.

Black-Schaffer, Kerby and Hiebert (1946) have recently reported that living organisms recovered from a case of purpuric meningococcemia, after two washings in normal salt solution, possessed the ability to prepare the skin of rabbits and elicit the Shwartzman phenomenon upon intravenous injection. When the organisms were heat-killed, they still retained these properties. Contrary to Shwartzman's experience, they found that the washed organisms were even more potent than the supernatant fluid. They

concluded that purpuric meningococcemia suggests a spontaneously occurring Schwartzman reaction, with the organisms present in the purpuric lesions as the probable counterpart of those that were intradermally injected in the rabbit and the meningococcemia as the probable counterpart of the provocative intravenous dose.

#### HETEROPHILE TOXICITY

Forssman (1911) discovered that the tissues of many species of animals, e.g., guinea pig, horse, cat, possess an antigen which, when injected into an animal whose tissues do not possess it, e.g., rabbit, will cause the animal to produce antibodies that are capable of causing hemolysis of sheep red blood cells. The antigen, because of its apparent heterogeneity, has been called heterophile antigen and the antibody engendered heterophile antibody. The heterophile antiserum of the Forssman type, in addition to other properties, possesses toxicity. When it is injected intravenously into animals whose tissues contain the Forssman antigen, it produces symptoms analogous to anaphylactic shock, the animals dying with post-mortem findings of hemorrhage in the lungs, liver, and kidney capsule. When injected intracutaneously, it causes a characteristic local edema and necrosis. A reverse heterophile toxicity may also be produced. If a rabbit which has reacted to injections of heterophile antigen, e.g., sheep red cells, by producing a high-titered heterophile antiserum is later injected with heterophile antigen even from another source, e.g., guinea pig kidney, it will react with symptoms of heterophile toxicity.

It is possible that the mechanism of Forssman heterophile toxicity is the same as that of anaphylaxis. However, heterophile toxicity differs from anaphylaxis in several respects.

1. Intoxication with heterophile antiserum causes more extensive edema and hemorrhage in the lungs.
2. Animals cannot be desensitized to the toxic effects of the antiserum.
3. The uterine muscle of a normal guinea pig fails to contract when exposed to the heterophile antiserum.
4. When injected in the skin of a guinea pig, the heterophile antiserum causes a characteristic local necrosis.
5. The most significant factor in the cause of death in heterophile toxicity is the rapidly increased permeability of endothelial linings and cell membranes.

The Forssman heterophile antigen is found widely distributed in many mammals, birds, fish, and bacteria, and is a primitive biological characteristic not associated with phylogenetic development. The bacteria which have been found to possess the heterophile antigen include the pneumococcus, green streptococcus, hemorrhagic septicemia group, *Neisseria catarrhalis*, *Bacillus anthracis*, *Shigella dysenteriae*, *Salmonella paratyphi*, *Clostridium perfringens*, *Clostridium oedematiens*, *Bacillus cereus*, *Bacillus megatherium*, *Bacillus petasites*, and *Alcaligenes faecalis*.

It would appear then that antisera against heterophile-containing bacteria produced in animals (rabbits) which do not possess heterophile antigen would be dangerous to use in animals whose tissues possess Forssman antigen or in human beings belonging to blood groups A and AB (their red cells possess Forssman antigen), whereas similar antisera produced in animals whose tissues or red cells possess the Forssman antigen could be used with safety in all animals. On the other hand, animals whose tissues do not possess heterophile antigen and human beings belonging to types B and O (possess no Forssman antigen) could develop the heterophile antibody as a result of infection with microorganisms containing the antigen. Such individuals, if later vaccinated with organisms containing heterophile antigen or if given horse serum (contains some heterophile antigen) might react with symptoms of heterophile toxicity, the degree of the reaction depending upon the amount of heterophile immune body present in the individual. This could account for the toxicity of horse serum in some cases.

## SUMMARY

Of the five types of bacterial hypersensitiveness which have been discussed, three (anaphylaxis, atopy and heterophile toxicity) do not differ materially from their prototypes to nonbacterial agents. The other two (tuberculin-type and Schwartzman-type) have thus far been induced and elicited only with microorganisms and their products. It is possible that underlying all types of hypersensitiveness is a common basic principle, namely, that the exposure of the tissues to an undigested foreign or abnormal substance stimulates the production of a specific antibody, different for each substance, and that the different forms of hypersensitivity reaction are effects that result from the interaction of antibody and antigen under different conditions.

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### THE ASTHMATIC CHILD: A SCHEME FOR THE TREATMENT OF CERTAIN NON-SPECIFIC FACTORS. I. Mirvish: *South African M. J.*, 19:186-187, (June 9) 1945.

The author states that certain non-specific factors, such as emotional disturbances and fatigue, cannot only of themselves precipitate the asthmatic attacks, but failure to handle this aspect of the problem can completely wreck the most carefully devised scheme of medical treatment. The child as well as the disease must be treated. This demands a knowledge of the whole psychological background of the child—his relation to his parents, brothers and sisters, family, school teachers, and friends. The family practitioner, who occupies the role of "guide, philosopher and friend," is in the best position for studying the child in his environment, and the knowledge so gained when properly applied is of the utmost value in treatment.

The author gives an outline for a questionnaire with respect to the parents, the child, and school. He also gives some general instructions. The first of these is for the parents to be patient. There is no quick road to recovery, and ups and downs are to be expected. The parents are warned that the child is easily affected by the attitude of people about him. A cheerful, happy atmosphere tends to keep the condition in check, whereas an atmosphere of anxiety, nervousness, or tension is liable to precipitate an attack at any age.

As far as possible, the use of the term "asthma" or "attack" either in the presence of the child or others is to be avoided, and the child's ailments should not be discussed with other people, particularly in his presence, nor should he be compared with other children in his own presence.

The child should be encouraged to sleep alone. During an actual attack, excitement and panic are to be avoided. If the child is wheezing very mildly, do not draw his attention to it as this emphasis is almost certainly likely to make the attack worse. Fatigue must be guarded against. The commonest causes of chronic fatigue in a school child are: (a) insufficient rest; (b) irregular feeding habits; (c) too many "extras"—music lessons, dancing, et cetera.

The child must be treated, as far as possible, not as an invalid, but as a normal child.

# CHEMICAL, PHYSICAL AND IMMUNOLOGICAL PROPERTIES OF ELECTROPHORETICALLY PURIFIED POLLEN EXTRACTS

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IN the past decade, notable achievements in the fields of physics and physical chemistry have given the biologist and the physician new tools to scrutinize more closely the relation of the constitution of matter to the causation of disease. In particular, the use of the electrical field and the gravitational field to analyze the movements of molecules has led to a deeper understanding of the size of proteins and of antigens in general. Among the new devices in particular are:

- (a) Tiselius' moving boundary method of electrophoresis.
- (b) The ultracentrifuge.
- (c) Precision diffusion devices easily manipulated.

By means of these techniques, it has been made possible for my co-workers and myself to isolate, in the purest form apparently achieved thus far, the main colorless constituents found in pollen extracts of giant ragweed, dwarf ragweed and of timothy grass.<sup>1-10</sup> In addition, certain of the chemical and immunological properties of these major colorless molecules, as well as of the pigmented molecules, have been characterized. It has been found that the molecules responsible for clinical, pollen hay fever and asthma are not the large protein antigens which had hitherto been thought to be the specific immunological factors involved. Rather, my co-workers and I were surprised to find consistently that in these pollen extracts, as well as in all the other pollen extracts studied by us, the excitants of the symptoms of pollinosis were comparatively small molecules, having molecular weights not much more than 5,000, and having properties similar to but not characteristic of proteins. These molecules which have been isolated in highly purified form have been named as follows:

(a) In giant ragweed pollen (*ambrosia trifida*), the main constituent has been called "Trifidin."

(b) In dwarf ragweed pollen (*ambrosia artemisiaefolia*), the main constituent has been called "Artefolin."

(c) In timothy pollen (*phleum pratense*), the main colorless constituent is now named, for the first time, "Pratensin."

## METHODS

Figure 1 illustrates the moving-boundary method of Tiselius. The main portion, that is the side-arms and the connecting tubes, are merely electrode vessels. The actual electrophoretic separation of the

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This research was aided in part by a grant from the Josiah Macy, Jr., Foundation.

molecules occurs in the U-tube itself, which is in the central and lower part of the figure.

Figure 2 gives the dynamic process occurring in the electrophoresis cell with a three component mixture. Let us assume that three different

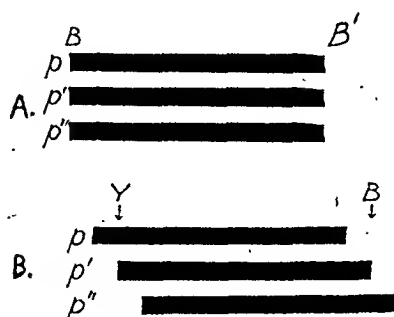
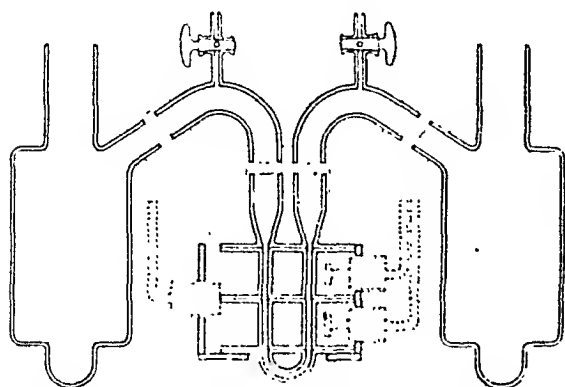


Fig. 1. (left) The moving-boundary method of Tiselius is illustrated in general. Note the large electrode arms and the small central U-tube with sliding sections. It is by means of these sliding sections that isolation of electrophoretically homogeneous fractions can be readily obtained.

Fig. 2. (right) This visualizes the dynamic process occurring in the electrophoretic cell with a three component mixture in the U-tube itself at the boundaries. When the uniform electric field is applied, proteins of different electrical mobility move at different speeds. By suitable sampling devices, the following fractions can be obtained: (a) Electrophoretically homogenous  $p$ . (b) Electrophoretically homogenous  $p''$ . (c) Mixed  $p+p'$ . (d) Mixed  $p'+p''$ . For further understanding of this process, see Figure 3.

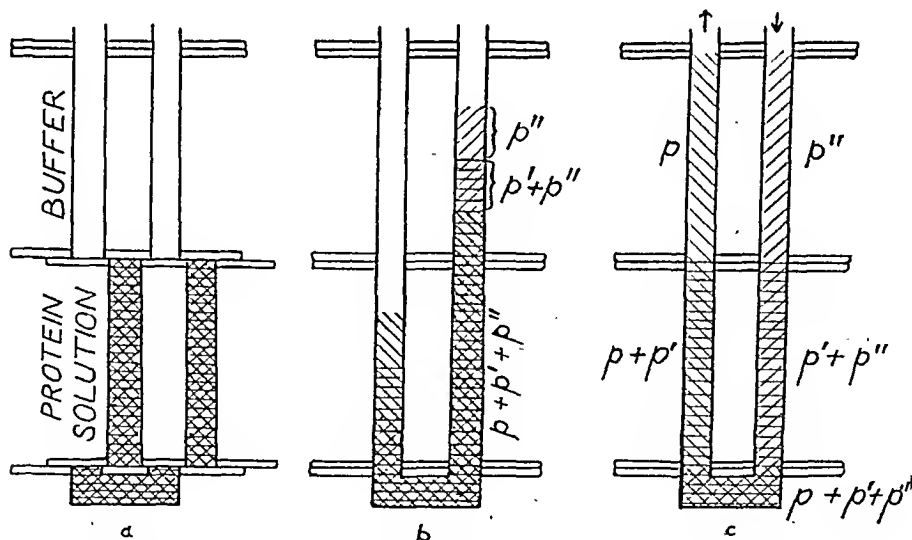


Fig. 3. The dynamics of electrophoretic fractionation is shown in the U-tube. Refer to Figure 2.

electrically charged proteins are present, with varying electric mobilities. If a uniform electric field is applied, the components will be moved to a new position as indicated in Figure 2(b). It is evident that by making a segregation at Y and at B, a portion of protein  $p$  and of protein  $p''$  can be obtained in pure form. The same phenomenon occurs in the U-tube as illustrated in Figure 3. It was this technique, combined with special

optical methods of locating the boundaries which enabled us to isolate the main colorless constituents, Trifidin, Artefolin and Pratensin. In addition, it was this technique which also permitted the isolation of highly purified fast-moving pigments, especially in timothy pollen extracts.

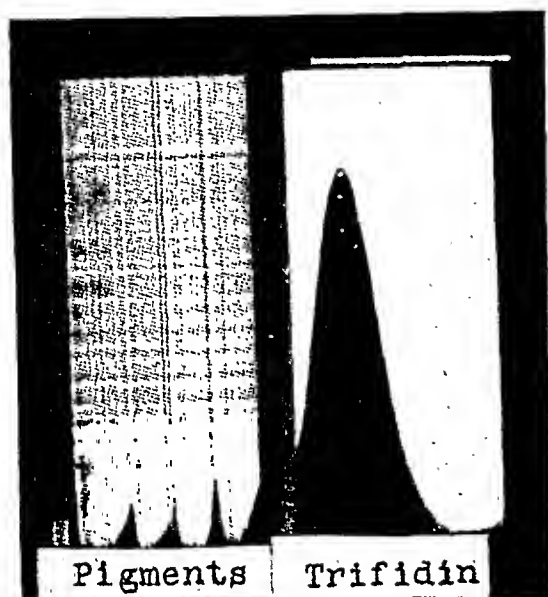


Fig. 4. The electrophoretic separation of the main colorless component Trifidin in giant ragweed pollen extract at pH. 6.5. The tall peak, labeled "Trifidin" is the main colorless component. The four smaller peaks on the left are produced by minor pigments. The actual electrophoretic migration occurs in a vertical position. The photograph has been rotated.

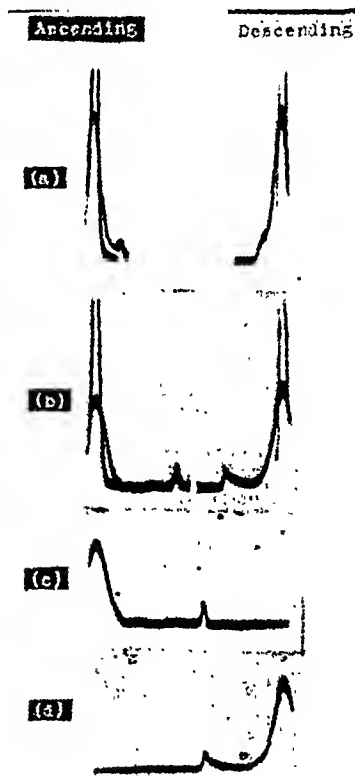


Fig. 5. The isolation of the fastest moving pigment in giant ragweed extract. This pigment is biologically active.

Indeed, it was possible to show that pigment fractions, free of the main components, Trifidin, Artefolin and Pratensin, gave skin reactions directly and by passive transfer.

#### ISOLATION AND IMMUNOLOGICAL PROPERTIES OF TRIFIDIN, ARTEFOLIN AND PRATENSIN

Figure 4 illustrates an experiment depicting the electrophoretic separation of the main colorless component, Trifidin, in giant ragweed extract. Illustrated also are four pigments. However, six or seven pigments have been observed and there is evidence that these are all biologically active.

Figure 5 illustrates the isolation of the fastest moving pigment in giant ragweed extract. This pigment is biologically active. In general, similar results were found for dwarf ragweed.

Figure 6 shows a successful electrophoretic analysis of timothy grass pollen extract with final isolation of Pratensin at the twenty-second hour.



As in the case of the ragweed extracts, there are numerous pigments labeled *p* in the figure. Similar results were found, but not without some differences, in the electrophoretic analysis of June grass, Bermuda grass, sheep sorrel, English plantain, birch and red oak. Indeed, our electro-

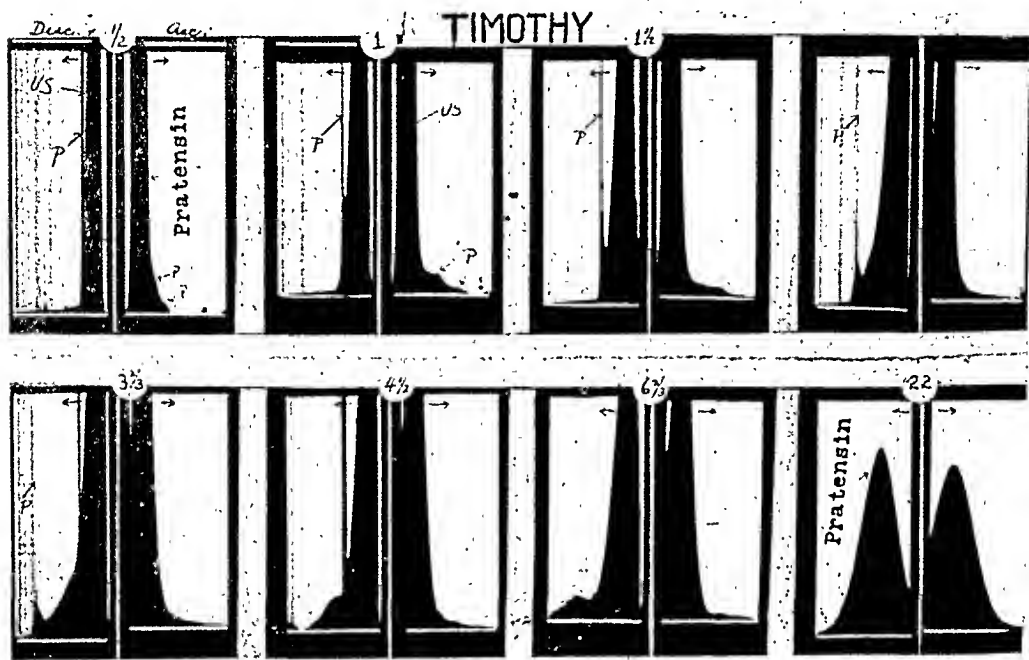


Fig. 6. The electrophoretic analysis of timothy grass pollen extract with final isolation of Pratensin at the twenty-second hour. Pratensin is the main colorless component. As in the case of ragweed extracts, numerous minor pigments are present. These are labeled *P*.

phoretic analysis showed a general similarity of all of the patterns with main colorless constituents and minor pigmented fractions, the activity of which, based on the evidence obtained thus far, indicates biological activity in both the pigmented molecules and the pigment-free colorless components.

#### ULTRACENTRIFUGAL AND DIFFUSION STUDIES ON TRIFIDIN AND ARTEFOLIN

As indicated in the foregoing, the electrophoretic technique enabled us to isolate the main colorless components of giant and dwarf ragweed pollen solutions. However, the size of the molecules was uncertain. We knew that these molecules were biologically active and, in addition, they diffused through ordinary collodion membranes. To obtain the approximate size of the molecules, the rate at which these molecules sedimented in the ultracentrifuge was ascertained. Figure 7 illustrates the actual sedimenting boundaries of Trifidin and Artefolin, compared with crude solutions of giant and dwarf ragweed themselves. Figure 8 shows the rates of sedimentation. Note that these molecules sediment out much more slowly than serum albumin. By correlating the ultracentrifugal data with diffusion studies, it was found that these molecules had molecular

weights of about 5,000 each. A molecular weight of 5,000 is rather low for the molecular weight of a typical protein. Indeed, considering the chemical reactions which will shortly be presented, it would appear that these molecules are closer to high-molecular-weight polypeptides, are more

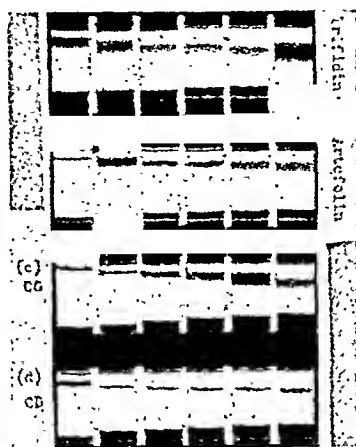


Fig. 7. The actual sedimenting boundaries of Trifidin and Artefolin in the ultracentrifuge are compared with crude pollen extracts of giant and dwarf ragweeds. The rates of sedimentation are almost the same.

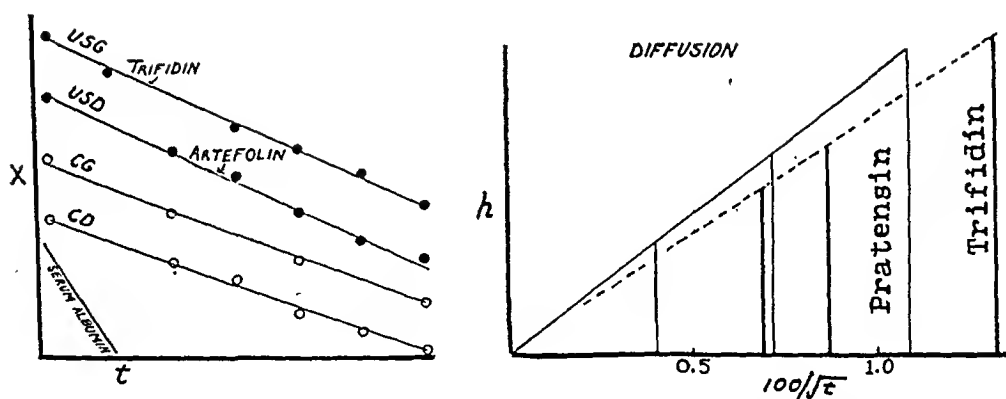


Fig. 8. (left) The rates of sedimentation of the boundaries in Figure 7 are plotted and compared with serum albumin. Note that serum albumin sediments in the gravitational field much more rapidly than Trifidin and Artefolin. This indicates that Trifidin and Artefolin have molecules which are comparatively smaller.

Fig. 9. (right) The diffusion rate of Pratensin is approximately the same as Trifidin, indicating that the molecular sizes are close to one another.

diffusible than proteins, can permeate the living system more readily, and show greater stability in the presence of heat.

Pratensin was also studied in the ultracentrifuge, but its molecule was not sedimented under the conditions of experiment. Diffusion studies, however, as illustrated in Figure 9, show that the molecule of timothy diffuses quite as rapidly as that of ragweed and, in all likelihood, has about the same molecular weight.

# POLLEN EXTRACTS—ABRAMSON

## CHEMICAL ANALYSIS

The war interfered with more detailed studies of the chemistry and immunology of these highly purified fractions of pollen extracts. However, some experiments were performed. These results (Table I) compare the reactions of Trifidin and Artefolin with serum diluted 1:30. In

TABLE I. REACTIONS OF TRIFIDIN AND ARTEFOLIN ISOLATED BY ELECTROPHORESIS.

Test	Trifidin	Artefolin	1:30 Serum
Standing in ice box...	Usually clear	Precipitate may form	
Phosphotungstic acid	Heavy precipitate	Heavy precipitate	Light precipitate
Millon .....	Positive	Positive	Positive
Biuret .....	Positive	Positive	Positive
Xanthoproteic .....	Deep yellow	Positive	Deep yellow
Trichloroacetic acid	Slight turbidity	Turbidity	Precipitate
Sulfosalicylic acid	Turbidity	Turbidity	Precipitate
Heller test .....	Slight opalescence	Slight opalescence	Positive
Heat and acetic acid	Opalescence	Opalescence	Opalescence
Molisch .....	Positive	Positive	

Note the lack of precipitation by trichloroacetic and sulfosalicylic acids.

our opinion, these reactions indicate that Trifidin and Artefolin are high-molecular-weight polypeptides, coupled with other molecules more or less formed like carbohydrate molecules, and that much more careful chemical work will be required on these fractions to determine their precise chemical nature. It is this type of experimentation, however, that will lead to the explicit evaluation of a chemical structure of a pollen antigen molecule.

## DISCUSSION

### *Relationship of Molecular Size To Ease of Sensitization.*

The general similarity of all of the electrophoretic patterns and the diffusion curves studied thus far indicates that we have to do with a new class of allergenic molecules, characterized by a molecular weight intermediate between those of typical proteins and polypeptides. Since the allergenic molecules are small, it is easy to understand how they can permeate the mucous membranes of the nose and other parts of the respiratory tract, to set up local and general allergic sensitivity. It is of interest to speculate that if the molecular weights of these allergenic molecules were 5,000,000 instead of 5,000, the frequency with which sensitization would occur should be much less because of the increased difficulty with which they would permeate the mucous membranes of the respiratory tract.

Rockwell,<sup>12</sup> using an independent method, has confirmed the molecular size reported here of these molecules. Further, Newell,<sup>11</sup> as well as Stone, Harkavy and Brooks,<sup>13</sup> among others, have all made important contributions to the chemical nature of allergenic molecules.

These and older investigations, having nearly all been recently surveyed in the excellent review of Wodehouse and Coca,<sup>14</sup> are not reviewed here.

*Relation of Multiplicity of Components in Crude Extracts to Standardizations.*

The experimental evidence unequivocally shows that pollen extracts are not simple antigenic solutions. They are complex mixtures, containing many components, the most different of which electrically, in the case of ragweed and timothy, are biologically active. The question arises: how justified is the position of those who insist that a chemical standardization procedure by phosphotungstic acid properly assays the biological activity of the extract? The implication contained in this point of view, that the phosphotungstic acid precipitable nitrogens of the various components are not only active but also equally active biologically, bears further scrutiny. I believe that the basic measure of allergic activity of a pollen extract must be a biological response; and only an immunological response like the eye, nose, or skin reaction measures in a sensitized case the activity of an extract. A chemical determination at best is a secondary reference and, with our present knowledge, cannot be considered a standardization procedure. At best, it is a method of convenience. Which of these chemical methods of convenience is preferable, is open to question.

*Future Investigations.*

The technique described provides the investigator with electrophoretically homogeneous fractions, both colorless and pigmented. By our technique, only the colorless fractions have been successfully centrifuged in the experiments thus far performed. Whether or not pigmented molecules have smaller molecular weights than the colorless molecules cannot be stated. The retardation experienced in the gravitational field could be due to the shape and electrification of the molecule as well as to a smaller size. Rockwell, however, believes that certain of the pigmented molecules studied by him have molecular weights of about  $1/5$  of the colorless components. As mentioned, the war interfered with our studies planned to investigate the detailed immunological properties of the electrophoretically purified fractions. Experiments with Dr. G. Schwartzman on animal sensitization had been started before the war. Similarly, there remain for further study:

- (a) The chemical characterization of the purified fractions.
- (b) The role in which the various purified fractions produce sensitization and protection, studied especially by means of the new techniques to assay the differences between the sensitizing and the inhibiting antibodies.
- (c) The interrelationships, both chemical and immunological, of the pigmented and the colorless forms.

It is only by the study of the characteristics peculiar to each component in the crude extract that basic immunological relationships can be established.

SUMMARY

1. The moving-boundary method of electrophoresis, the ultracentrifuge and diffusion techniques have been used to isolate and characterize the most highly purified fractions of pollen extracts thus far obtained.

2. It has been found that the molecules responsible for clinical, pollen hay fever and asthma are not large protein antigens but rather comparatively low-molecular-weight molecules, of the order of 5,000 or less, with chemical properties similar to but not characteristic of proteins.

3. Preliminary immunological and clinical studies indicate that pollen extracts are complex mixtures of many components with, however, a main colorless component readily isolated by means of the electrophoretic technique.

4. The main colorless component of giant ragweed extract has been named Trifidin, that of dwarf ragweed extract, Artefolin, and that of timothy extract, Pratensin. The relationship of the experiments described to the ease of sensitization, the standardization of crude extracts, and future experimental work, is briefly outlined.

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## REPORT ON THE STANDARDIZATION OF DUST EXTRACTS

ADVISORY COUNCIL OF THE STANDARDIZATION COMMITTEE

GEORGE E. ROCKWELL, M.D., Chairman

J. WARRICK THOMAS, M.D.

FRED W. WITTICH, M.D.

THE Standardization Committee of the American College of Allergists was organized for the purpose of studying various methods of standardizing allergenic extracts.

More than a year ago this committee began a co-operative research program on the preparation and standardization of house dust extracts. This was the first extensive co-operative research ever undertaken in allergy. The program called for the preparation, chemical analysis, and skin testing of a series of extracts; and it was hoped that the data accumulated would indicate a practical and satisfactory method of standardization. Reports of the progress of the committee have appeared from time to time as editorials in the *ANNALS OF ALLERGY*,<sup>6,7</sup> and now sufficient data has been collected to permit a complete review of this work.

Samples of house dust were supplied by members of the Board of Regents of the College, and we wish to thank Drs. Hal M. Davison, French K. Hansel, Merle W. Moore, Harry L. Rogers, J. Warrick Thomas, Leon Unger, Orval R. Withers, and Fred W. Wittich for their co-operation in furnishing this material.

All of these dust samples were sent to Dr. Rockwell, and the extracts were prepared, chemically analyzed, sterilized, cultured for sterility, bottled, and distributed from his laboratory at Milford, Ohio.

To provide complete information on these extracts, we felt that they should be tested for skin reactivity on patients in various sections of the country; therefore, members of the College practicing in all parts of the United States, as well as some from Canada, Cuba, and Mexico, assisted in the clinical testing.

From the eight different samples of house dust we made twenty-four different extracts, thirteen of which were distributed to be tested for skin reactivity. A total of 365 patients were tested, and 3,224 individual skin tests were made. The following thirty doctors participated in the clinical testing: Drs. Wyndham B. Blanton, Ethan Allan Brown, Gerald M. Cline, Hal M. Davison, G. Estrada de la Riva, Stephan Epstein, Royal H. Finney, H. Harold Gelfand, Jerome Glaser, George A. Gray, O. C. Hansen-Pruss, Robert F. Hughes, M. Salazar Mallen, James A. Mansmann, John and William Mitchell, Merle W. Moore, Homer E. Prince, George E. Rockwell, Harry L. Rogers, Jacob W. Schoolnic, Willard S. Small, Robert Stier, J. Warrick Thomas, Leon Unger, Erich Urbach, Ira Wickner, Orval R. Withers, Fred W. Wittich, and Pearl Zink. We gratefully acknowledge their assistance.

## DUST EXTRACTS—ROCKWELL ET AL.

### PREPARATION OF THE EXTRACTS

*Crude Extract.* Two hundred or more grams of house dust were placed in a large flask and extracting fluid added to it. This solution contained 9 grams NaCl, 20 c.c. normal NaOH, and 1 c.c. of 10 per cent merthiolate per liter. Since the house dust samples varied a great deal, some were easily wet by the solution while others required twice as much liquid; enough was always used to completely wet the dust. It was allowed to extract at a cool temperature for forty-eight hours; then filtered through a Buchner funnel.

*Crude Concentrate.* The crude dust extract was concentrated by evaporation under vacuum or by placing it in cellophane tubing and passing dry air over it. After it was concentrated it was briefly and rapidly dialyzed against distilled water to remove the excess salt.

*Alpha Picoline Concentrate.* Alpha picoline was added to the concentrated crude extract until maximum precipitation occurred. This precipitate was collected, and then reprecipitated one or more times with alpha picoline or further purified by means of ammonium sulfate. In many respects the alpha picoline acts as acetone does, but is superior to it in most ways except for the disagreeable odor.

*Absorbed Concentrate.* The crude extract was concentrated and then made distinctly acid with HCl after which it was treated with an absorbing agent such as Lloyd's reagent or certain of the filter aides. The absorbing agent was then filtered off, washed with acid solution, and added to an extracting fluid which had a slightly alkaline pH. This eluted the absorbed material from the absorbing agent. Such a preparation can be further purified by reabsorbing or by means of ammonium sulfate. The pH of the final preparation can be adjusted to neutrality and concentrated to the desired strength.

*General Procedure.* All of the dust extracts were Seitz filtered and cultured for sterility. At least six cultures were made from each extract using deep tubes and bottles of dextrose infusion broth. All extracts were diluted with 50 per cent glycerine by volume, then bottled under sterile conditions, and labeled.

### IDENTIFICATION OF EXTRACTS

As each extract was prepared, it was assigned a symbol which was used for identification of the extracts sent out for testing. In this way there was no possibility of favoring one extract over another in reporting results and each extract could be judged fairly on its own merits. Samples of Endo's House Dust Extract were also bottled, given symbols, and sent out for testing along with the newly prepared extracts. The following key is furnished for identification of the extracts.

# DUST EXTRACTS—ROCKWELL ET AL

## KEY FOR IDENTIFICATION OF DUST EXTRACTS

<i>Source of Dust Sample</i>	<i>Symbol for Dust Extract</i>	<i>Identification</i>
Dr. Davison, Georgia	DA	Crude concentrate
	DB	A-picoline concentrate
Dr. Hansel, Missouri	HB	Crude concentrate
Dr. Moore, Oregon	MA	Crude concentrate
	MB	A-picoline concentrate
Dr. Rogers, Pennsylvania	RB	Crude concentrate
Dr. Thomas, Virginia	TB	A-picoline concentrate
	TD	Crude concentrate
Dr. Unger, Illinois	UF	Crude concentrate
Dr. Withers, Missouri	WX	Absorbed concentrate
	WY	Crude concentrate
Mixed Dust	AA	Absorbed concentrate
	AB	Crude concentrate
Endo's House Dust Extract	DC	
	MC	
	RA	
	TA	

## CHEMICAL ANALYSIS OF EXTRACTS

All solutions were brought to 20° C. for volumetric measurement. All determinations were made in duplicate.

*Determination of Total Nitrogen.* The total nitrogen determinations on these extracts were made by the micro Kjeldahl method, using a small sample, preferably .5 to 1 c.c. This determination was made before the glycerine was added.

*Determination of Phosphotungstic Acid Precipitate Nitrogen.* This determination can be made before or after glycerine is added.

Ten c.c. of extract were precipitated with 5 c.c. of concentrated HCl and 5 c.c. of phosphotungstic acid reagent (10 per cent phosphotungstic acid in 10 per cent HCl). It was mixed thoroughly in a centrifuge tube and allowed to stand for 24 hours at near freezing temperature. The precipitate was separated by centrifugal force, and the supernatant fluid was tested with more concentrated HCl and phosphotungstic acid reagent to be sure that all of the phosphotungstic acid nitrogen had been precipitated.

The precipitate was then washed with 2 c.c. of a cold solution of ammonia-free water containing the same proportion of HCl and phosphotungstic acid reagent as were used for precipitation. It was chilled again, separated, and the supernatant fluid decanted. This was repeated once. Then the sides of the tube and surface of the precipitate were rinsed with 2 c.c. of cold ammonia-free water.

Two c.c. of ammonia-free water and one drop of phenolphthalein indicator were added to the precipitate. Enough NaOH was added to completely dissolve the precipitate, and after it was entirely in solution, a drop of acetic acid was added, or enough to make it definitely acid; then



it was washed into a 25 c.c. volumetric flask and diluted to volume with ammonia-free water.

Total phosphotungstic acid precipitate nitrogen was determined by the micro Kjeldahl method, using a 2 c.c. sample.

Free alpha amino nitrogen of the phosphotungstic acid precipitate was determined by the Van Slyke manometric method, using a 5 c.c. sample. Before determining the unknown sample the accuracy of the apparatus should be checked by running a known solution of glycine (1 mg. per c.c.).

*Determination of Molecular Size.* The phosphotungstic acid precipitate has erroneously been referred to as the protein nitrogen. Unfortunately this precipitate brings down not only proteins but peptides of all sizes and certain basic amino acids. Hence, it does not represent protein nitrogen but rather a mixture of any proteins (if present), peptides of all sizes, and certain amino acids (if present). But in dust extracts it is the best method available for separating peptides and any proteins from the other nitrogenous material present. Therefore, we shall consider the phosphotungstic acid nitrogen as the total nitrogen of the antigens present in dust extract.

Peptides, polypeptides, and proteins each have one free alpha amino nitrogen per molecule. Therefore, by dividing the total nitrogen of the phosphotungstic acid precipitate by the free alpha amino nitrogen we find the number of nitrogen atoms present in each molecule of the peptide or protein. This indirectly gives information on the size of the molecule present. Such calculations will be in error in proportion to the amount of nonspecific substances present in the phosphotungstic acid precipitate, and any specific antigen present which may not have been precipitated by the phosphotungstic acid.

#### TESTING AND EVALUATION OF EXTRACTS

*Method of Testing Extracts.* In order that the testing of these extracts be uniform, a set of directions for skin testing was prepared by the Advisory Council of the Committee. The directions set forth were as follows:

1. All tests are to be made intradermally.
2. Please keep antigens in refrigerator when not being used.
3. Use properly cleaned and sterilized sharp 26-gauge hypodermic needles and tuberculin syringe.
4. The amount injected should be constant and accurately measured for all tests, and recorded on the data sheet.
5. The dilutions to be used will be indicated in the letter sent out with the extracts.
6. Injections: Make injections approximately 2 inches apart with the least possible trauma in the volar surface of the forearm and lateral surface of the arm. Injections are preferably made by the same individual so that the technique will be about the same.
7. Reactions: Skin reactions may be read with a 75-watt Mazda lamp or by daylight. Observations of the skin reactions should be made at fifteen minutes and readings taken about twenty minutes after the injections. When the wheals and

flares are of their maximum size they should be recorded by one of two methods: (a) Tracings: The wheals and flares are outlined on the skin with a washable ink. Thin tissue paper is placed over them and both the wheal formation area and erythema are traced in pencil. These tracings should then be transferred by means of carbon paper to the enclosed data sheet. (b) Measurements: The wheal and flare should be measured in centimeters and recorded as wheal/flare; for example, a wheal measuring 1 x 1 cm. with a flare of 2 x 4 cm. should be recorded as 1x1/2x4. A notation of "ps" should be made if pseudopodia develop; thus, if there were pseudopodia, it would be recorded as 1x1/2x4 ps.

Each doctor was asked to make four dilutions of the extract: namely, 1:10, 1:100, 1:1000 and 1:10,000. The house dust-sensitive cases were to be tested with all four dilutions and the controls with the 1:10 and 1:100 dilutions. The results were recorded on special sheets furnished for the purpose.

*Method of Evaluating Skin Reactions.* The following system was devised for the evaluation of skin reactions:

1. Only the wheal was considered.
2. The wheal was carefully measured in millimeters and the average diameter computed.
3. If the amount of extract injected was .01, .02, or .03 c.c., no consideration was given to it; however, if .05 c.c. was injected, the average diameter of the wheal was divided by 2.
4. The highest dilution was considered first; if the wheal measured less than 5 mm. in average diameter, it was disregarded and the next lowest dilution was judged and so on.
5. Scale of values:

<i>Dilution</i>	<i>Average Diameter of Wheal in Millimeters</i>	<i>Rating of Skin Reactivity</i>
	10 or more.....	6
1:10,000	8 or 9.....	5
	5, 6, or 7.....	4
1:1,000	5 or more.....	3
1:100	5 or more.....	2
	3 or 4.....	1

## RESULTS

We felt that the simplest way to present the results of such an extensive experiment would be to assemble the data in charts and tables, each designed to illustrate or prove a point in question. This we have endeavored to do.

*Comparison of Total Nitrogen and Skin Reactivity.* Table I shows the total nitrogen and skin reactivity of five different dust extracts. Note that the total nitrogen varies greatly and compare this variation to the skin reactivity.







From these results it is obvious that total nitrogen content and skin

reactivity of an extract have no direct relation to each other. This lack of correlation is emphasized by the fact that several of our extracts with widely different total nitrogen content gave almost identical skin reactions.

TABLE I. NO DIRECT RELATION BETWEEN TOTAL NITROGEN CONTENT AND SKIN REACTIVITY OF A DUST EXTRACT

Dust Extract	Total Nitrogen mg. per c.c.	Rating of Skin Reactivity
AA	0.3594	4.12
WX	0.3722	5.00
RB	0.8200	4.11
UF	1.6010	3.90
WY	2.1277	4.85

TABLE II. DUST EXTRACTS WITH WIDELY DIFFERENT TOTAL NITROGEN CONTENT GAVE ALMOST IDENTICAL SKIN REACTIONS IN PATIENTS\*



















Extract	Patient: S. S.	Patient: T. A.
AA  1:100 Dilution  Total Nitrogen 0.3594 mg. c.c.		
WX  1:100 Dilution  Total Nitrogen 0.3722 mg. c.c.		
WY  1:100 Dilution  Total Nitrogen 2.1277 mg. c.c.		

\* Tests done by Dr. Salazar Mallen.

This is shown in Tables II and III with tracings of individual skin reactions.

From Tables II and III one notes that in the four extracts the total nitrogen varies from 0.3722 to 2.1277 mg. per c.c., yet the skin reactions are identical within experimental error.

TABLE III. DUST EXTRACTS WITH WIDELY DIFFERENT TOTAL NITROGEN CONTENT GAVE VERY SIMILAR SKIN REACTIONS IN PATIENTS\*

Extract	Patient: Mrs. L. F.			Patient: Miss M. M.		
	Dilutions of Extract			Dilutions of Extract		
	1:100	1:1,000	1:10,000	1:100	1:1,000	1:10,000
WX Total Nitrogen 0.3722 mg./c.c.						
RB Total Nitrogen 0.8200 mg. c.c.						
WY Total Nitrogen 2.1277 mg. c.c.						

\* Tests done by Dr. S. Epstein.

*Comparison of Skin Reactivity and Phosphotungstic Acid Precipitate Nitrogen.* Cooke<sup>4,5</sup> has contended that the phosphotungstic acid precipitate nitrogen of pollen extracts contains the active antigen. Although this has been questioned by others<sup>1,2,3</sup> and may not be absolutely true, it still remains the most practical and convenient method of separating the active antigens from the crude dust extracts. If the antigens of all dust extracts are exactly alike, then standardization by the total nitrogen of the phosphotungstic acid precipitate should be accurate; and this total nitrogen should have a definite sequence with the amount of skin reactivity of such antigens.

Table IV lists eleven extracts with increasing amounts of phosphotungstic acid precipitate nitrogen; however, there is no uniformity or regular sequence in the molecular size of the antigens. In this group the number of nitrogen atoms varies from 4 to 14 per molecule.

From this table it is evident that the skin reactivity rating does not absolutely follow the variations in the phosphotungstic acid precipitate nitrogen although it does so more than it follows the total nitrogen content.

*Molecular Size.* In contrast to the preceding experiment, six extracts were selected whose antigens were approximately the same molecular size, varying only from 9 to 14 nitrogen atoms per molecule. These extracts were diluted so that the phosphotungstic acid precipitate nitrogen was con-

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stant at .300 mg. per c.c. From these we made dilutions of 1:100 and 1:1,000 which were sent out for skin testing. Each patient was tested with all six of the extracts in both dilutions, thus the results make it possible to

TABLE IV. SKIN REACTIVITY OF DUST EXTRACTS IN  
RELATION TO THEIR PHOSPHOTUNGSTIC ACID  
PRECIPITATE NITROGEN CONTENT, BUT  
NOT IN RELATION TO THEIR  
MOLECULAR SIZE.

Extract	Phosphotungstic Acid Precipitate Nitrogen mg. per c.c.	Rating of Skin Reactivity
TD	0.1360	3.60
DB	0.1407	3.76
AA	0.3064	4.12
WX	0.3238	5.00
AB	0.3710	4.37
TB	0.5346	4.00
MA	0.5515	4.05
RB	0.7065	4.11
MB	0.8530	4.47
UF	0.9680	3.90
WY	1.2843	4.85

TABLE V. SKIN REACTIVITY OF DUST EXTRACTS  
WHICH CONTAIN EXACTLY THE SAME AMOUNT  
OF PHOSPHOTUNGSTIC ACID PRECIPITATE  
NITROGEN AND IN WHICH THE ANTIGENS  
ARE APPROXIMATELY THE SAME  
MOLECULAR SIZE.





































Extract	Phosphotungstic Acid Precipitate Nitrogen mg. per c.c.	Rating of Skin Reactivity
AA	0.300	3.57
RB	0.300	3.71
UF	0.300	3.57
WX	0.300	3.52
MB	0.300	3.47
MC	0.300	3.52

compare these extracts one with another. Table V shows these results.

From Table V it is apparent that when dust extracts are selected so that the molecular size of the active antigen is approximately the same, the skin reactivity is dependent upon the phosphotungstic acid precipitate ni-

trogen. In other words, dust extracts standardized on a molar basis can be made identical so that their skin tests are identical. To further illustrate this, Table VI shows tracings on three different patients with this series of extracts.

TABLE VI. TRACINGS OF SKIN REACTIONS WITH DUST EXTRACTS WHICH CONTAIN EXACTLY THE SAME AMOUNT OF PHOSPHOTUNGSTIC ACID PRECIPITATE NITROGEN, AND IN WHICH THE ANTIGENS ARE APPROXIMATELY THE SAME MOLECULAR SIZE\*

Extract	Patient: L. L.		Patient: R. D.		Patient: M. DeB.	
	Dilutions of Extract 1:100	1:1,000	Dilutions of Extract 1:100	1:1,000	Dilutions of Extract 1:100	1:1,000
AA						
RB						
UF						
WX						
MB						
MC						

\* Tests done by Drs. G. A. Gray and G. E. Rockwell.

































*Effect of Regional Distribution on Skin Reactivity.* The samples of dust used in this work were collected in various parts of the country, and the extracts made from them were skin tested in numerous places, which afforded an opportunity to study the effect of regional distribution. Table VII lists the source of the extract and the testing regions together with the rating of skin reactivity in each region. All of the extracts were sent to doctors in various regions, however, some did not respond, hence this summary is not complete.

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TABLE VII. SIX SOURCES OF DUST SAMPLES LISTED IN THE VARIOUS STATES IN WHICH THEY WERE TESTED, TOGETHER WITH THEIR RATING OF SKIN REACTIVITY IN THAT STATE.

Georgia	Virginia	Missouri	Illinois	Oregon	Pennsylvania
Canada 3.6	Va. 3.6	Ohio 2.6	N.Y. 3.7	Oregon 4.6	Penna. 4.2
Penna. 3.4	Mass. 3.4	Oregon 2.2	Ohio 4.2	Ill. 3.0	Ohio 2.6
Wash. 3.9	Ohio 4.8	Cuba 3.0	Penna. 3.8	Texas 4.2	Oregon 3.7
	Mo. 4.6		Texas 3.6	N.C. 3.0	Wisc. 5.0
	Texas 3.5			Minn. 5.3	
	Calif. 4.0				

TABLE VIII. INDIVIDUAL VARIATIONS IN SKIN REACTIONS\*

Extract	Case 1			Case 2		
	Dilutions of Extract			Dilutions of Extract		
	1:100	1:1,000	1:10,000	1:100	1:1,000	1:10,000
RA						
RB						
TB						
TD						
DA						
DB						

\* Tests done by Drs. W. F. Mitchell, O. R. Withers, and R. F. Hughes.

Table VII shows that although there is some variation from region to region it is not as great as one might expect. Undoubtedly an active dust extract will give a positive skin test in any section of the country.

*Individual Variations in Skin Reactions.* Although there is not much variation in skin reactivity in one region as compared to another, we have










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repeatedly noticed in this collective study that there are many individual variations in skin reactions. We have selected a few reports to illustrate this point in Table VIII.

TABLE IX. SKIN REACTIVITY OF ALPHA PICOLINE CONCENTRATES COMPARED TO CRUDE CONCENTRATES.

Extract	Phosphotungstic Acid Precipitate Nitrogen mg. per c.c.	Rating of Skin Reactivity	Rating of Skin Reactivity of the Corresponding Crude Concentrate
DB	0.1407	3.76	3.69
TB	0.5346	4.00	3.60
MB	0.8530	4.47	4.05

TABLE X. TRACINGS OF SKIN REACTIONS WITH THREE DIFFERENT ALPHA PICOLINE CONCENTRATES\*

Extract	Dilutions of Extract		
	1:100	1:1,000	1:10,000
TB			
DB			
MB			

\* Tests done by Drs. R. F. Hughes, O. R. Withers, and F. W. Wittich.

You will note from this table that in one case one extract appears to be stronger and in another case the results are reversed, thus emphasizing individual variation.

*Dust Extracts Purified and Concentrated by the Alpha Picoline Method.* These extracts are potent and are an improvement over the crude concentrates. This is shown in Table IX, in which we have tabulated a few of



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them together with the concentrated crude extract made from the same dust sample.

From Table IX it is noted that the alpha picoline extract has more skin

TABLE XI. AMOUNT OF PHOSPHOTUNGSTIC ACID  
PRECIPITATE NITROGEN AND THE SKIN RE-  
ACTIVITY OF TWO ABSORBED CONCENTRATES AND ENDO'S DUST EXTRACT.

Extract	Phosphotungstic Acid Precipitate Nitrogen mg. per c.c.	Rating of Skin Reactivity
AA	0.3064	4.12
WX	0.3238	5.00
Endo	0.4090	4.25

TABLE XII. TRACINGS OF SKIN REACTIONS WITH  
TWO DIFFERENT ABSORBED CONCENTRATES\*

Extract	Dilutions of Extract		
	1:100	1:1,000	1:10,000
AA			
WX			

\* Tests done by Drs. W. B. Blanton and S. Epstein.

reactivity than does its corresponding crude concentrate. This is further illustrated in Table X, which shows individual tracings of typical skin reactions due to alpha picoline extracts.

*Extracts Purified and Concentrated by the Absorption Method.* The skin reactivity ratings of these extracts together with their phosphotungstic acid precipitate nitrogen contents are shown in Table XI along with Endo's for comparison.

From Table XI it is noted that although the phosphotungstic acid precipitate nitrogen in the preparations purified and concentrated by the absorption method is much lower than that of Endo's extract, the skin reactivity is approximately as high in one instance and higher in another

than is Endo's. Thus it is evident that these extracts are potent and biologically active.

To further illustrate this, Table XII shows actual tracings of tests done with extracts purified and concentrated by the absorption method.

From Table XII it is evident that these extracts purified and concentrated by absorption are capable of giving good wheal reactions in sensitive cases.

#### CONTROLS

In any skin test the matter of control must be considered. Controls for a series of tests such as we are reporting might be divided into two groups: (a) nonallergic controls and (b) allergic but clinically nondust-sensitive controls.

We felt that if the concentrated dust extract was to mean anything it should give a positive test in at least a 1:100 dilution in a dust-sensitive patient; and correspondingly should give a negative test in 1:100 dilution in a control. Therefore, our controls were tested in a dilution of 1:100. However, this may lead to confusion because one extract may be much more concentrated than another and a 1:100 dilution of it would be a stronger extract than a 1:100 dilution of the other. The responses on our questionnaire were not sufficient for us to divide our cases into nonallergic controls and allergic patients who were nondust-sensitive, therefore, we shall have to consider them as a whole.

Our crude concentrated extracts tested 40.5 per cent negative and 59.5 per cent positive (rating of 1 and occasionally of 2) in the controls. The picoline concentrates gave 45.5 per cent negative reactions and 54.5 per cent positive; whereas our absorbed concentrates gave 57.9 per cent negative and 42.1 per cent positive reactions. In comparison, Endo's dust extract sent out under code symbol gave 51.7 per cent negative and 48.3 per cent positive reactions in the controls.

As mentioned above, however, one cannot accept these figures exactly on their face value. If we arbitrarily conclude that a 1:100 dilution should contain .003 mg. phosphotungstic acid precipitate nitrogen per c.c., then on such basis our crude extract was a dilution of 1:67 and not 1:100. Our absorbed concentrate still remains 1:100, whereas the picoline concentrate would be a dilution of 1:59 and Endo's would be a dilution of 1:73. Recalculated on this basis our results would be: Crude concentrate gave 40.5 per cent negative skin reactions in a dilution of 1:67; picoline concentrate gave 45.5 per cent negative in a dilution of 1:59; absorbed concentrate gave 57.9 per cent negative in a dilution of 1:100; and Endo's extract gave 51.7 per cent negative in a dilution of 1:73.

What these extracts would have shown in the controls had they all been diluted to contain .003 mg. phosphotungstic acid precipitate nitrogen per c.c. (our theoretical 1:100 dilution) is hard to estimate. Again, what constitutes a negative reaction needs to be more clearly defined, and this

will undoubtedly require further studies. From our work on this experiment we would conclude that the smallest positive reaction should be a wheal of at least 5 mm. diameter in a dilution of 1:100. However, it is evident that our crude concentrated extracts gave a higher percentage of positives in controls than did Endo's; our absorbed concentrates definitely gave fewer positive reactions in the controls than did Endo's; and our picoline concentrates gave approximately the same number of positives as did Endo's.

#### STANDARDIZATION

We feel that any standardization of dust extract must be done both biologically and chemically. Specifically we recommend that standardization of dust extract give the following information: (1) the total nitrogen, (2) the phosphotungstic acid precipitate nitrogen, and (3) the relative number of nitrogen atoms per molecule of antigen. And we recommend that the dust extract should meet the following specification: when it is diluted to contain .003 mg. phosphotungstic acid precipitate nitrogen per cubic centimeter it should give a positive reaction in known dust-sensitive cases and a negative reaction in known controls.

This data furnishes the following information: (1) the amount of non-specific nitrogen present, namely, the difference between the total nitrogen and the phosphotungstic acid precipitate nitrogen; and (2) the relative number of molecules of active antigen present and also the relative size of these molecules. The skin tests will tell whether or not the antigen is biologically active, and the controls will show whether or not there is any nonspecific reaction present.

Some people feel that standardization of dust extracts is not necessary and possibly even undesirable. We question very much if it is possible to make two dust extracts exactly alike unless they are standardized by both chemical and biological methods. We doubt very much if there is any dust extract on the market which, lot after lot, bottle after bottle, will be exactly the same. For instance, in our experiments we sent out Endo's extract under code number to the various testing members. All of the samples sent out were from one lot so that all results would be uniform. However, some of the members, not knowing that Endo's was among the extracts they were testing, tested with their Endo's and sent back reports that were different from the Endo's which they unknowingly tested in code number. This prompted us to obtain another lot and analyze it chemically. The lot that we sent out contained .409 mg. phosphotungstic acid precipitate nitrogen per c.c. whereas the second lot contained only .310 mg. per c.c.

#### SUMMARY AND CONCLUSIONS

Methods are given for preparing the extracts known as crude concentrate, alpha picoline concentrate, and absorbed concentrate; also the various methods of analysis are given.

Data is presented which definitely shows that there is no relation between skin reactivity and the total nitrogen present in an extract. Evidence is presented which shows that although there is some relation between skin reactivity and the phosphotungstic acid precipitate, nitrogen, it at best is not too good when there is appreciable variation in the molecular size of the dust antigen. However, when extracts were selected whose antigens were of approximately the same molecular size, and when they were adjusted so that the phosphotungstic acid precipitate nitrogen was constant, their skin reactivities were alike within the limit of the experimental error of such tests. Evidence is presented showing the skin reactivity of dust collected in various parts of the country and then subsequently tested in various regions. The variance indicates that there is not as much discrepancy in skin reactivity between the various sections of the country as there is in individual variations.

It is concluded that extracts, purified and concentrated with alpha picoline or by the absorbed method, are potent extracts, with characteristics which improve them over crude extracts or any other extracts to which they have been compared.

It is concluded that successful standardization of dust extract can be done by a combination of chemical and biological methods. The standardization chemically involves the determination of total nitrogen; and the total and free alpha amino nitrogen of the phosphotungstic acid precipitate. It is pointed out that such extracts should then be tested biologically and dilutions be made based upon their chemical analysis—namely, dilutions so that the extract contains .003 mg. of phosphotungstic acid precipitate nitrogen per cubic centimeter. Such an extract should be capable of giving a positive reaction in a known dust-sensitive case and a negative reaction in a normal individual.

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## CLINICAL AND COMPARATIVE ALLERGY

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MODERN medicine is built on a fundamēt of experimentation. Experimentation is observation under controlled conditions. And man is both the most desirable and for obvious reasons the least available subject of experimentation. For this reason, one of the most important steps in the development of modern medicine was the recognition of the concept of the essential similarity of the organization of all living matter. This would sound trite were it not for the fact that allergy is usually treated as if it were an affliction particular to the human race. Zinsser<sup>10</sup> formulated this notion very prettily when he said that man "possesses an immaculately conceived type of sensitivity, that, like his soul, distinguishes him from the animal kingdom." This certainly is a prejudice. We have a number of reports on allergic diseases in animals—particularly horses, cattle and dogs.<sup>14</sup> Some reports may not be as well substantiated as is expected in human medicine. Others are. A good example is F. W. Wittich's study and presentation of a dog with hay fever.<sup>15</sup> L. Reddin, Jr.,<sup>11</sup> and R. Povar<sup>9</sup> presented interesting clinical observations today. Allergists have reason to be grateful for those papers because they concern a point vital for the speedy development of allergy. For good measure, I am showing the head of a walrus baby, which was observed by C. R. Schroeder<sup>12</sup> for a skin infection resembling eczema. This walrus baby was bottle fed, and Dr. Schroeder at once had the correct conception of the nature of the disease. He suspected that it might be connected with the unnatural food, and he was able to prove this point. He put the little walrus on a fish diet, and the eczema promptly improved. This is a remarkable case, one of the earliest clear-cut observations in any animal and, as far as I am aware, still the only one in a wild animal. But beyond that, I wish that allergists would remember this head each time they wonder about the basic problems of allergy. I want it remembered as a symbol that our friends, the animals, are ready to help in the exploration of allergic phenomena just as much as in other problems of physiology and pathology, if we only are willing to ask them the right questions.

As a matter of fact, the history of supersensitivity starts with animals because anaphylaxis was first observed in goats and dogs. And it then turned out that the guinea pig had been created especially for the purpose of anaphylactic experimentation. Anaphylaxis, of course, is different in important but not basic aspects from other phenomena of supersensitivity. Experiments in anaphylaxis have been done on a number of species, as guinea pigs, rabbits, rats, mice, and dogs. But experi-

Read at the meeting of the American College of Allergists, San Francisco, California, June 28 to 30, 1946.  
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mentation on other forms of supersensitivity have been done in the main on the guinea pig. Dermal sensitization to various antigens and haptens can be classically demonstrated and studied in the guinea pig, and the same is true with tuberculin sensitivity.<sup>1,8</sup> If one adds the work on the



Fig. 1. Head of the milk allergic walrus baby (courtesy of Dr. C. R. Schroeder).

sensitization of rhesus monkeys by Straus and Coca,<sup>13</sup> the work in cattle on sensitization to ragweed,<sup>14</sup> and the work on serum sickness in rabbits by Fleischer and his co-workers,<sup>4</sup> the list is almost exhausted. Thus, it is small wonder that allergy has not harvested the benefits other fields of medicine have derived from experimentation. However, as allergic edema, eczema and hay fever have been found in other animals, it should be possible to select the proper animal for experimentation of the various problems causing concern. Moreover, from what data there is, it appears likely that where local allergic sensitization is passively transferable, this transfer can be effected from one species to another. This should greatly facilitate the comparative evaluation of observations in different species. Altogether, a whole nearly unexplored field of research is open here for the mutual benefit of human and veterinary medicine, promising a harvest valuable in itself and able to create tools for experimentation.

To enlarge a little on some of the problems waiting for the proper experimental approach, those of heredity are of particular importance. Present knowledge of the hereditary factors in allergy is general, rather than detailed. In animals bred for utility, for example, one would expect that breeding tends to eliminate inherited allergic factors. On the other hand, it is remarkable how many of the reports on allergy in animals refer to inbred stock. Dr. Povar's experience<sup>9</sup> in this respect

is quite characteristic. Systematic exploration of the hereditary factors in animals would certainly be an object in fundamental interests. Landsteiner<sup>8</sup> was one of the first to realize that. In his laboratory Chase<sup>1</sup> was able to show that in guinea pigs, within a few generations, the propensity to become sensitized can be greatly enhanced. The use of stock selected from this point of view has greatly contributed to the success of the work of Landsteiner and Chase. It is of particular interest that guinea pigs selected by sensitization to dinitrochlorobenzene were also found to be more uniformly sensitized to poison ivy and, inversely, a stock of low susceptibility to dinitrochlorobenzene was inferior in ability to become sensitized to picrylchloride. It appears also that the Rockefeller stock is of high susceptibility to anaphylactic sensitization.<sup>2</sup> Though these data do not concern a highly inbred strain, and despite the circumstance that Chase noted several exceptions to the rule, the general trend of the experience is akin to that in man. Namely, what is inheritable in allergy is not so much the propensity of acquiring sensitization to a given antigen, but the general propensity to sensitization as such, or rather the propensity to acquire a certain class of sensitization. Coca's data<sup>3</sup> indicate that certain types of sensitization may have an independent mechanism of inheritance. No doubt it would be most fascinating if this could be confirmed and elaborated upon by experimentation.

Another problem awaiting analysis by experimentation is that of sub-clinical sensitization. When testing cows with ragweed extracts,<sup>10,14</sup> we found 40 per cent definitely skin-sensitive, but there was no indication of clinical affection. This is an observation of some clinical interest because positive skin tests without clinical manifestations are well known to every one of us, and we all know that they constitute a considerable source of incertitude and a frequent source of error. We are maybe a bit too much inclined to avoid this problem by just labeling such reactions as unspecific. I, personally, and I am sure a great many others, will have our doubts whether a competently made skin test—a test performed with all necessary controls and precautions—is actually ever unspecific. It is easy to hide behind this word, but it would be better to spend some thought on the problem involved. To me, a much more likely working hypothesis would be that sub-clinical sensitization is very frequent. The epidemiologist will state that an exactly parallel situation exists in the field of infectious diseases. The number of actually clinically sick persons in a population may represent only a small percentage of those infected. Information on the mechanism of epidemics has greatly gained by the recognition of this fact. I would suppose that further experimental evidence of the frequency of subclinical sensitization may be very helpful in our attitude to clinical problems.

There is, furthermore, the whole complex problem of the mechanism of sensitization beyond the primary factor of antibody response to an antigen. This fundamental problem can only be approached properly

if the spade work has been done which will give the proper experimental setup.

As the last point, the question of the quantitative relations in allergic reactions should be mentioned, if only to lament our ignorance. It is known that extremely small amounts of antigen are needed both for shock and particularly for sensitization, but very little is clear about the quantitative relations between antigen and antibody even in those cases where circulating antibody has been demonstrated. The best approximation of such quantitative data is found in Kabat's work<sup>6,7</sup> on passive sensitization of guinea pigs. From these papers it appears that antibody in the order of 0.5 mg. per kg. body weight will sensitize practically 100 per cent of the animals. This figure looks rather small. However, if one considers that the antibody, like a drug, must localize in the body's cells, it becomes apparent that this figure is well within the order of magnitude of effective doses for numerous pharmacologically active compounds as, for instance, atropine and digitalis. Moreover, the effective antibody dose is calculated for total body weight, and there is good reason to believe that antibody molecules are not fixed in the body at random, but are concentrated in certain cells.

The antigen-concentration necessary for shock was found by Kabat to be several milligrams per guinea pig and this was found to be true for a proteinic antigen (crystalline ovalbumin) and a carbohydrate (pneumococcal S-substance). This means a dose in the order of 10 mg. per kg. body weight is needed. The randomness of antigen distribution is not known. However, the fact that it is immediately effective for shock makes it likely that it is more evenly distributed than is the antibody, which has to be fixed by the cells, as testified by the period of lag which is in the order of many hours.

Kabat feels that his figures suggest that optimal conditions for anaphylaxis are found in the region of considerable excess of antigen. Because of the uncertainty concerning the randomness of distribution, I feel that this conclusion is not yet proven. If antibody is concentrated in relatively few cells—what has been called shock tissue—a fraction only of the antigens circulating in the blood may be available for reactions, and this would possibly shift the ratio of antigen nearer to the point of equivalence known from *in vitro* measurements. This view is also supported by an evaluation of the data which were obtained in neutralization tests in the skin of cattle.<sup>14</sup> In this case one can calculate that antibody in the order of micrograms neutralized 5 to 25  $\mu\gamma$  of the ragweed extract. If it is taken into account that the unpurified extract used certainly contains only a small percentage of active antigen, one immediately sees that in this case of a local effect there could be present no considerable excess of antigen.

In his papers, Kabat points out that the concentrations of immune antibody necessary for anaphylactic sensitization are well below those



needed for the formation of visible precipitates in the test tube. Accordingly, he proposed as a working hypothesis that the lack of visible *in vitro* reaction of serum from allergic diseases may be explained by a mere concentration factor. In other words, he suggests—as have others (Zinsser)—that quantitative considerations may offer an alternative to the usual conception that allergic antibodies are qualitatively different from immune antibodies. The difference between immune and allergic antibodies in heat stability, in local fixability in the tissue, and in ability to passively sensitize the guinea pig's smooth muscles, militate against such a viewpoint. It remains, however, worthwhile to look for direct evidence for or against the quantitative alternative. It appears quite possible that the refinement in the determination of antibodies worked out in recent years in Heidelberger's laboratory may be of great help for this purpose. This method<sup>5</sup> allows one to measure with considerable exactitude amounts of antibody in the order of micrograms.

The scientific program of the American College of Allergists emphasizes work on the purification of antigens. Progress in this field will be a most important complement to the experimental exploration of the quantitative relations.

I hope that this summary of the present knowledge of allergy in animals and its relation to medical allergy will demonstrate the desirability of building up this field of endeavor. Allergy is not an affliction peculiar to man, and a realization of this cannot but be helpful in making the whole complex field appear as the expression of a basic physiological mechanism. The few examples given here will encourage our faith that systematic experimentation in animals will become eventually as important a complement to clinical observations as it has proven to be in other fields of medicine.

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# HAY-FEVER PLANTS OF ALBUQUERQUE, NEW MEXICO

## A Preliminary Report

WALTER I. WERNER, M.D., F.A.C.A., WILLIAM G. REED, B.S., and

E. L. STORMFELS, A.B.

Albuquerque, New Mexico

THIS is a report on the 1945 hay-fever season for Albuquerque, New Mexico. Its purpose is to outline the hay-fever problem for an area of mild and arid climate to which many sufferers come seeking relief from respiratory ailments.

Although the literature on hay-fever plants is replete with regional reports (Wodehouse,<sup>5,6</sup> Gottlieb and Urbach<sup>2</sup>), the problem varies from locality to locality. In the existing literature the states of New Mexico, Arizona and western Texas are treated regionally as the Southwest. Texas and Arizona have a reasonable presentation of local problems done by various authors. However, only one area thus far has been reported for New Mexico, Gallup by Watry and Lamson.<sup>4</sup>

The variety of the flora in New Mexico, especially in Albuquerque and the Rio Grande River valley, presents a serious and complicated hay-fever problem. The present report presents the species of pollen present, as nearly as possible, the exact beginning and ending of the pollination period of each, and their clinical significance in Albuquerque.

Albuquerque stands at an altitude of 5,000 feet in the Rio Grande valley. The river flows west of the city swinging southward to El Paso, Texas. Twelve miles east of the city, the rim of the Sandia Mountains stands 10,678 feet above the valley floor. A tableland or "mesa" slopes gradually from the base of the mountains to the river valley which is from two to three miles wide with a floor of hard clay, sand and gravel. Many sandy arroyos or dry stream beds cut through the gravelly soil of the mesa.

Precipitation in the valley averages 8 inches a year, which is sufficient to support little more than a desert flora, while in the mountains it is greater, probably 32.6 inches a year, sufficient to support a mixed forest. The forest floors in the mountains contain much humus and retain the moisture, resulting in heavy growths of timber, particularly on the east slope of the Sandias on the far side from the city. The mesa soil contains no humus, consequently has no capacity for holding moisture.

Most of the grasses, weeds and trees involved in the hay-fever problem in and around Albuquerque were found accompanying the irrigation systems, in the borrow ditches along the highways which collect the rain draining from the pavements, and in areas where the water table has been brought close to the surface by irrigation ditches or the river.

From The Maytag Research Laboratories of the Southwestern Presbyterian Sanatorium, Albuquerque, New Mexico.

TABLE I. HAY-FEVER PLANTS OF ALBUQUERQUE, NEW MEXICO  
Field Observations—1945  
Plants listed as to season and major and minor causes of hay fever

SPRING		SUMMER		FALL		WINTER	
MAJOR	MINOR	MAJOR	MINOR	MAJOR	MINOR	MAJOR	MINOR
<i>Trees</i> —Early and late flowering species		<i>Trees</i> —Late flowering species	<i>Trees</i> —Late flowering species	<i>Trees</i>		<i>Trees</i> —Early flowering species	
Juniper	Elm		Pine		none		Elm
Cottonwood	Tamarisk		Locust				
	Oak		Mulberry				
	Ash		Tree of heaven				
	Maple		Tamarisk				
	Pine						
	Locust						
	Catalpa						
<i>Grasses</i>		<i>Grasses</i>		<i>Grasses</i>		<i>Grasses</i>	
Bermuda	Johnson	Bermuda	Blue	Bermuda	Johnson		
	Brome		Johnson		Finger		none
	Blue		Western June		Grama		
			Salt sacatone		Salt sacatone		
<i>Weeds</i>		<i>Weeds</i>		<i>Weeds</i>		<i>Weeds</i>	
	Plantain	Russian thistle	Plantain	Russian thistle	Wingscale		Russian thistle (only slight)
		Lambs quarters	Lambs quarters	Pigweed	Amaranthus		
		Amaranthus	Amaranthus	False ragweed	Burning bush		
		Burning bush	Burning bush	Redsage	Redsage		
		Redsage	Redsage	Pasturesage	Pasturesage		
		Shadescale	Shadescale	Bur ragweed	Bur ragweed		
		Pasture sage	Pasture sage	Sagebrush	Sagebrush		
		False ragweed	False ragweed	Cocklebur	Cocklebur		
				Lambs quarters	Lambs quarters		

The valley has a comparatively low mean annual range of temperature (55.6°F.) and a daily high range. Over a period of 50 years the average daily maximum temperature for June was 88.2°F. and the average minimum 58°F., giving a range of 30.2°F. The average date of the first killing frost is October 28 and the last, April 13. This gives an average of 198 frost-free days which tends to produce a long pollinating period.

Albuquerque is in the "Sunshine State." The annual average amount of sunshine is 76 per cent. As a result of the regular sequence of the climatic influence the plants flower and fruit with clock-like regularity.

Wind is another factor having effect on the production and distribution of pollen. Wind increases the evaporation of moisture from the soil and plants, consequently the spring season which is the windiest is the driest. The prevailing winds blowing to Albuquerque area from the south and southwest, sweep over broad expanses of arid caprock mesas, spotted with scrubby juniper trees, and carry away from the city the pollens of the trees and plants which grow in the more verdant high altitudes of the mountains. Because high winds aid in the dissemination of pollen, the pollen counts taken during the months of March, April and May were the highest for the year. However, the species of pollen found were of little importance in hay fever.

Two-thirds of the area of New Mexico is representative of the Upper Sonoran zone, and comprises plains, and foothill country ranging in elevation from 4,500-7,500 feet. This is the zone of junipers, nut pine and blue grama grass. This mesa formation is characterized by low rainfall, and sparse vegetation consisting chiefly of desert shrubs (mostly composites), yuccas and short grasses.

The Transition zone covers the greater part of the Sandia mountains. It is a wide and continuous zone at approximately 7,500-9,500 feet elevation. This is the zone of the principal timber trees of the state.

The methods followed in making this study were essentially those of the average pollen survey. We are primarily interested in the anemophilous plants, and their pollen in the atmosphere. Four stations were established, and for each, the hay fever plants were listed, within a radius of 100 feet to 5 miles, their time of flowering noted, and samples of their pollen collected for making reference slides. These collecting and field stations were distributed in the city as follows: Station Number 1, State Health Laboratory, University of New Mexico, exposure 15 feet above ground, and known as the Heights District; Station Number 2, Maytag Research Laboratory, exposure 40 feet above ground, and representing the beginning of the downtown section; Station Number 3, United States Weather Bureau, Albuquerque Airport, exposure 30 feet above ground, covering the flat mesa area; Station Number 4, Rio Grande Boulevard near Old Town, exposure 4 feet above ground, representing the river area.

The gravity method for collecting pollen was used. The adhesive on

the microscope slides was glycerine-jelly with methylgreen. Each slide was kept in an exposed horizontal position with no protective shelter for twenty-four hours before being removed and studied. Throughout this study, the method of counting pollen as outlined by Dahl and Ellis<sup>1</sup> was used. It is called, "The Unit Area Basis," and represents the most practical standard. It is the number of pollen grains per square centimeter of surface of the exposed microscope slide determined either by direct observation or by derivation from the number of grains counted in 25 systematically distributed microscopic fields (low power, 100X). The latter calculation may be made as follows:

Area of 1 microscopic field (low power) expressed in sq. mm. x 25 = total area examined (in sq. mm.).

The monthly values stated are the average of data collected at the four stations, graphically presented as a total pollen count. At all times, plants were collected and identified, and correlated with the pollen counts. The data of these stations varied, but it is assumed that the average of observation at these four localities represents average conditions prevailing in Albuquerque and environs.

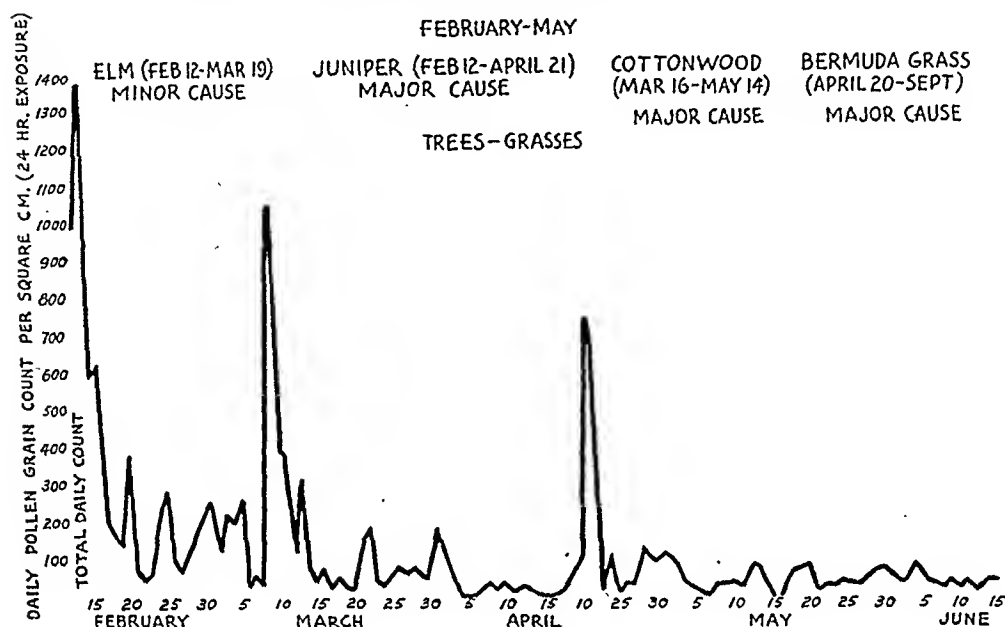
Each month is considered separately as a chronological record of the hay-fever plants and analyzed as to the species of pollen making up the total count for that particular month. As the survey was started in the middle of February, we have no data on the pollen counts for the first six weeks of the year. However, depending upon our study of the trees and climatic factors, there was a slight possibility during that period of early spring trees pollinating, such as the elm and cedar\*. Both American elm and Chinese elm pollinated profusely in February. The Chinese elm is a widely planted shade and ornamental tree in and around the city and accounts for the high pollen count of this period; but elm pollen is only a minor factor in clinical hay fever. There are a number of species of junipers growing around Albuquerque. However, the total pollen count for the junipers was not high during the month.

During the month of February our data revealed a close correlation between meteorological factors and the daily pollen count, with one exception. Warm days during early spring speeded up pollen production. High winds aided its dissemination. On cold days the count was noticeably low, on warm days high. Elms continued pollinating all through March and into April, along with juniper, Arizona cypress and arbor vitae. Juniper (*J. monosperma*, *J. scoparius*) was the most abundant plant pollinating in March. Field studies revealed that other trees beginning to pollinate were ash, cottonwood and willow. Pollen identification was difficult but juniper was found on the slides from the 9th of March throughout the month. Cottonwood pollen was first observed on the slides about March 16, increasing as the season progressed.

\*In our 1946 pollen counts, February 19 was the onset of tree pollination.

As the meteorological factors became more constant in March, they showed less influence on the total pollen count. It was noted that weather factors as a whole (other than wind velocity, perhaps) had less and less effect on pollen dissemination as the summer approached.

CHART I. SPRING AND SUMMER HAY-FEVER SEASON



April brought severe hay fever in Albuquerque, and cottonwood was the primary offending pollen, although grasses and weeds began flowering during the month. Rising temperatures and spring winds combined to produce and disseminate the pollen.

The cottonwoods continued pollinating throughout April, and accounted for the majority of the pollen, with the highest daily count on the 21st at Station Number 1. The counts in the valley were lower, and the anthesis somewhat later than at the stations higher up in the mesa, with the exception of Station Number 4, which fitted in with the retarded pollination of some species in the valley due to the temperature inversion. Some juniper pollen was still in the air, but of no clinical moment. The Chinese and American elm had undoubtedly completed pollination, although an occasional grain was found now and then. Ash, boxelder and willow pollinated in limited amount throughout the entire month, but none of their pollen was trapped on the slides. It played no part in the tree hay fever here.

The grasses began flowering in mid-April complicating the work of identification of the pollen grains on our slides. It was almost impossible to identify those of grass without going into the field and making reference slides directly from the plants. This work had to be continued until

the end of the hay-fever season in October to make certain the identification of pollen from an increasing number of plants. Blue grass or June grass (*Poa pratensis*) began flowering about the 15th of April, and Bermuda grass (*Cynodon dactylon*) about the 20th. These are not range grasses, but are widely planted in Albuquerque lawns. Blue grass and Bermuda grass make up most of the lawns in the city and, of all the hay fever grasses, Bermuda is considered the greatest offender.

In April, many herbaceous flowers and shrubs, both cultivated and wild, made their appearance, also the flowering of oaks. The only oaks near Albuquerque are scrub oaks (*Quercus gambelii*) in the foothills of the Sandias, and while they probably were pollinating, none of their pollen was observed on the slides, probably because the prevailing winds carried it away from the city.

Among the weeds, English plantain (*Plantago lanceolata*), which is considered to be of some importance as an irritant, began pollinating during the last week in April. Again, as with the grasses, there was pollen from the weeds which was not recognized, and it was necessary to go into the field to make reference slides.

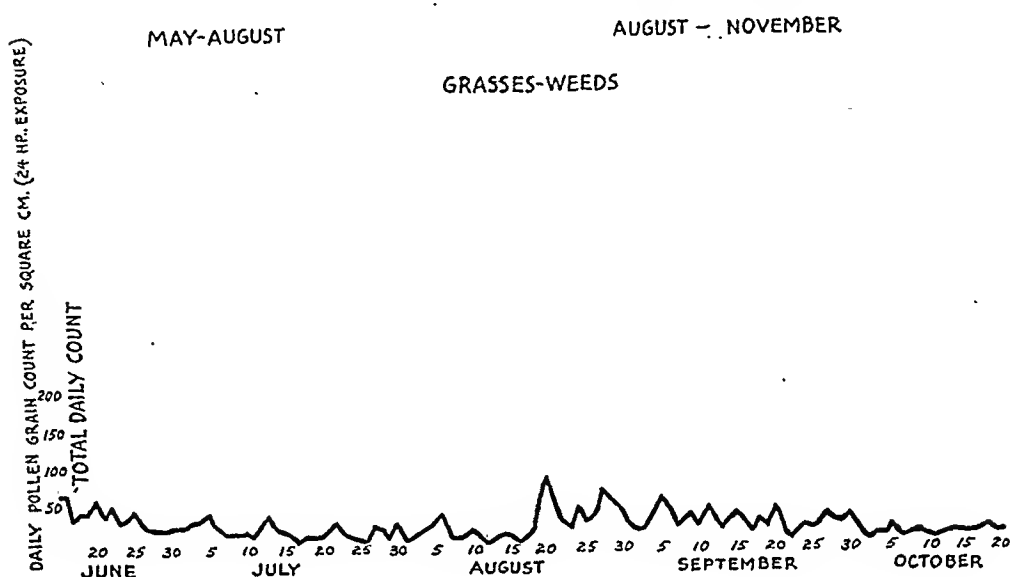
Rain and cold weather showed their usual effect in limiting pollination early in April, while warmer temperatures and winds which came later in the month aided both the production and dissemination of the pollen. The pollen count was low for the first few weeks of April, gradually rising, reaching its peak on the 21st of the month, when temperatures and wind velocity were high.

Compared with the preceding months, the total pollen count for the month of May was very low (1289) although there was a greater diversity of species. This period marks the end of the tree season, and the beginning of that of the summer pollinating plants. Trees are essentially early flowering plants, and it should be noted that they are the only species flowering before the average date of the last killing frost (April 13). The first plants to flower after this date are the early grasses such as Bermuda and Johnson grass, which might be considered indeterminate plants because of their long period of flowering.

While May is a transition period between the flowering of late spring and early summer plants, it is nevertheless marked with a diversity of pollen species resulting in difficulty of microscopic identification. We found grasses and weeds appearing in abundance. From then on they constituted the chief source of annoyance to the hay-fever sufferer. This was true especially of Bermuda grass, which flowered profusely during the whole month and continued all summer into the fall season. Other grasses such as June grass, Johnson grass, brome and perennial rye grasses were flowering, but these were of minor importance. Weeds, as a group generally are considered serious offenders. Pigweed (*Amaranthus retroflexus*), observed the last week of May, continued to flower until early fall. Lambsquarters also was noted at this period but not

in abundance. Russian thistle (*Salsola pestifer*), which is the most abundant and worst offender, began flowering at the end of May, and continued until a late hard killing frost. Plantain or buckhorn (*Plantago lanceolata*), while not very abundant, was found in flower on most lawns

CHART II. SUMMER AND FALL HAY-FEVER SEASON



throughout the month and continued to flower all summer. As the summer progressed, the diversity of pollen species increased.

June found the pollen count still declining (1108) although there was a larger variety of plants in flower at this time than at any other. The pollen count was uniformly low for July (497), so that this month is considered to be a continuation of the general summer hay-fever season. *Kochia scoparia* and *Kochia americana* were observed in the field. These are not very abundant, but have wide and spotty distribution over the city. No new pollens were listed for June, and none of the species pollinating earlier had ceased flowering.

The months of May, June and July may be considered together as the summer hay-fever season, with grasses and weeds the chief source of annoyance to the hay-fever sufferer. While the pollen count is low for this season, comparatively speaking, the species are of much greater toxicity. The chief offenders are Bermuda grass, Russian thistle and plantain.

The total pollen count in August (692) was about one third greater than that of the previous month, probably because of the beginning of what might be termed the fall hay-fever season, with the appearance of several new species, such as the sagebrushes, ragweeds and late flowering grasses. The sagebrushes (*Artemisia*) probably constituted the most important group of hay-fever plants next to the ragweeds and pos-



sibly even the grasses. Fortunately, the sagebrushes do not occur in great abundance around Albuquerque. Both the false ragweeds (*Franseria*) and the true ragweeds (*Ambrosia*) made their appearance in August. Some workers have found the pollens of the different species of *Ambrosia* to inter-react more or less perfectly, so that sensitization to that of one of them implies more or less sensitization to that of the others. Therefore, while our ragweeds are not profuse, they are considered to be of some importance.

The September pollen count was slightly higher than that of August, but from September 20 it decreased gradually to zero. September marked the end of the flowering period for some of the hay-fever species, such as plantain, burweed, pigweed and Johnson grass. However, others, such as Russian thistle, common sunflower, the false and true ragweeds, cockleburrs, burning bush, redsage, several sagebrushes, as well as many composites and late flowering grasses continued their flowering all month.

There was a very pronounced drop in the total pollen count for the month of October (107), due in part to the precociousness of the season, as well as to the first killing frost of the year which occurred October 28, 1945. After this killing frost the weather became colder and very few plants survived. Only Russian thistle, Bermuda grass, a few sagebrush species and ragweed were observed after the last week in October, and these only in the more favored places. No new species made their appearance this month. The end of October terminated the fall hay-fever season bringing freedom from suffering for many hay-fever patients.

#### DISCUSSION-SUMMARY

Plants in the temperate climates show a marked tendency to flower and fruit only at certain periods of the year, depending on the length of day. The date of flowering in any locality, is very constant, especially in a climate as equable as that in Albuquerque, where meteorological factors vary but slightly.

After the first killing frost occurring about October 28, it was noticed that only a few species survived for a short time, and these only in warm and protected places; they had disappeared by November 7. Before the last killing frost of the spring, which is about April 13, the only species flowering were the trees which are hardy, such as the elm, and considered a minor offender in hay fever. The average frost period between these two dates is 167 days, and can be considered of no importance in hay-fever management. It is the frost-free period of 198 days, from April 13 to October 28, which constitutes Albuquerque's major hay-fever season.

*The Spring Season.*—From about February 12 to May 7, divided into early spring and late spring by the vernal equinox, March 21. The chief

(Continued on Page 57)

# Editorial

*The opinions expressed by the writers of editorials in the ANNALS are individual and do not necessarily represent the group opinion of the Board or of the College.*

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## CURRENT COMMENT ON ANTIHISTAMINE EFFECT

Recent experiments, designed initially to study the antihistaminic effect of pyribenzamine and benadryl, by Mayer and Brousseau, bring into sharp focus the inadequacy of the histamine theory of anaphylaxis. These investigators studied histamine poisoning in the mouse with previous administration of pyribenzamine and of benadryl. We quote from their paper:†

"If antihistaminic substances such as pyribenzamine or benadryl were given in subcutaneous injections of 10 or 25 mg. per kg. body weight fifteen minutes before the histamine injection, the toxicity of histamine was not decreased, as is usually the case with guinea pigs or dogs, but, on the contrary, was strongly enhanced. . . . Histamine phosphate alone in a dose of 375 mg. per kg. body weight was lethal for ten out of twenty-three mice (43 per cent). In combination with 25 mg. per kg. pyribenzamine, the same dose of 375 mg. of histamine killed sixteen out of sixteen mice (100 per cent), and in combination with 25 mg. per kg. benadryl, ten out of ten mice (100 per cent). . . . The dose of 25 mg. per kg. pyribenzamine, or benadryl is nontoxic for mice. . . .

"The results indicate that the increase in toxicity of histamine is proportional to the dose of pyribenzamine or benadryl previously injected. These surprising results indicate that pyribenzamine or benadryl, which strongly and specifically counteract and neutralize histamine in guinea pigs and dogs, are definite synergists of histamine in mice."

Somewhat contrary were the results with pyribenzamine and benadryl in anaphylaxis in mice, although no case was completely freed of all shock symptoms, even with high doses of pyribenzamine. Some protection was observed against convulsions and death. These experiments again emphasize the importance of obtaining quantitative data in man based upon a concept of clinical pharmacology, even though the authors emphasize that in the mouse the antihistaminic substances which they use were acting upon unusual systems. Certainly the pharmacological responses of man cannot be directly compared with those of laboratory animals. Particularly is this true where emotional factors influence the course of the disease. In view of the data of Mayer and Brousseau, it is not clear why it is desirable to emphasize the antihistaminic effects of benadryl and pyribenzamine rather than the depressive action.

H.A.A.

\* \* \*

Since the above was written, it has come to our notice that *Science*, in the December 6, 1946, issue, contains an item describing an exhibit of the

†Mayer, R. L., and Brousseau, D.: *Proc. Exper. Biol. & Med.*, 63:187, 1946.

Ciba Pharmaceutical Products, Inc., in which Pyribenzamine Hydrochloride was featured as follows:

"The featured product around which the exhibit is built is Pyribenzamine Hydrochloride. This preparation is a new antihistaminic compound of very high efficacy in the treatment of various types of allergy. Pyribenzamine is a synthetic drug, effective by mouth, and is therefore made available in the form of oral tablets. Its greatest success has been achieved in the treatment of seasonal allergic rhinitis (hay fever) and urticaria (hives). In these two conditions relief is obtained in approximately 85 to 95 per cent of cases. In bronchial asthma and nonseasonal allergic rhinitis the success rate is not quite as high but still remains impressive. Other and more rare forms of allergy are benefited in greater or lesser degree. Fortunately, serious undesirable side reactions from this drug are extremely rare. The exhibit depicts pictorially the dramatic effects of Pyribenzamine both in the laboratory animal and in the human subject."

There is accumulating evidence that these statistics are not based upon the experience of allergists as a whole. There is no doubt that the discovery of Pyribenzamine Hydrochloride is a step in the right direction, and Doctor Mayer is to be congratulated upon his contribution to its discovery. It will take another hay-fever season or two before any accurate evaluation can be made.

F.W.W.

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## THE VETERANS ADMINISTRATION AND ALLERGY

There has been considerable dissatisfaction expressed by members of the College concerning the way the Veterans Administration has been recognizing the importance of care of allergic veterans.

A uniform and adequate fee schedule for the care of veterans suffering from allergy is highly desirable. We understand that this matter is now being worked out in Washington by the Veterans Administration. Each state seems to have its own schedule of fees, based upon the State Committees on Medical Economics. This has led to absurd suggestions; for instance, in one state it is proposed that the asthmatic veteran be charged twenty-five dollars for inhalants and twenty-five dollars for food tests, which is another way of saying fifty dollars. Every asthmatic is entitled to an exhaustive investigation, and a uniform policy for the study of the allergic veteran should be in operation soon.

It is very evident, also, that the Veterans Administration, when appointing the Branch Section Chiefs, has openly showed favoritism toward one allergy society.

During World War II there was considerable evidence that personal prejudice and the opinions of one or two distinguished laymen entered into other branches of the Government when dealing with allergy. An example was the sudden closing of the Central Allergy Laboratories of the Fourth Corps Area under Col. Sanford French, which made allergenic

extracts. This station supplied allergenic extracts for many officers in charge of allergy stations all over the United States as well as the Pacific area, thus saving thousands of dollars for the government. These abuses call for a Congressional investigation in the near future.

Veterans are writing to the College secretary frequently, because of the attitude of the Veterans Administration toward compensation for allergies acquired while in the services. Some of these letters would make very interesting reading if presented before an investigation committee appointed by Congress.

F.W.W.

### Hay-Fever Plants of Albuquerque, New Mexico

(Continued from Page 54)

offenders are juniper, cottonwood and Bermuda grass in their respective pollinating periods, with some overlapping.

*The Summer Season.*—From about May 7 to August 7, divided into early and late summer by the summer solstice, June 21. While the pollen count, comparatively speaking, is low at this time of the year, toxic hay-fever plants are more profuse. The chief offenders are Bermuda grass, Russian thistle and plantain.

*The Fall Season.*—From about August 7 to November 7, divided into early and late fall by the autumnal equinox, September 21. Russian thistle, pigweed and western ragweed are the chief offenders.

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University of Kansas School of Medicine

Monday, May 5, 1947, to Thursday, May 8, 1947, Inclusive

At the University of Kansas Hospital,  
W. 39th St. and Rainbow Blvd., Kansas City, Kansas

Sponsored by the American College of Allergists

#### SCHEDULE OF COURSES AND FACULTY

Monday, May 5, 1947

A.M.

- 8:00- 9:00 Registration  
9:00- 9:10 Address of Welcome  
HARRY R. WAHL, M.D., Dean, School of Medicine, University of Kansas.  
9:10-10:00 Chemistry and Allergy  
RUSSELL C. MILLS, Ph.D., Assistant Professor of Biochemistry, School of Medicine, University of Kansas.  
10:00-11:00 Physiological Aspects of Allergy  
KENNETH E. JOCHIM, Ph.D., Professor of Physiology, School of Medicine, University of Kansas.  
11:00-12:00 Antigen-Antibodies as Related to Allergy  
NOBLE P. SHERWOOD, Professor of Bacteriology, School of Medicine, University of Kansas.  
12:00-12:15 Orientation—Chairman

P.M.

- 2:00- 3:00 Bacterial Allergy  
FRED W. WITTICH, M.D., Minneapolis, Minnesota  
3:00- 4:00 Diagnosis of Allergic Disease  
M. MURRAY PESHKIN, M.D., Instructor, College of Physicians and Surgeons, Columbia University.  
4:00- 5:00 Hay Fever—Diagnosis and Management in Children  
ALBERT STOESSER, M.D. Clinical Professor of Pediatrics, University of Minnesota, Director of Allergy Clinics at University Hospitals and Minneapolis General Hospital.  
5:00- 5:45 Hay Fever—Specific and Symptomatic Treatment  
LAWRENCE J. HALPIN, M.D., Cedar Rapids, Iowa

Tuesday, May 6, 1947

A.M.

- 9:00-10:00 Botany  
ROGER WODEHOUSE, Ph.D., Associate Director of Research in Allergy, Lederle Laboratories, Pearl River, New York  
10:00-11:00 Bronchial Asthma—Classification and Treatment  
LEON UNGER, M.D., Associate Professor, Department of Medicine, Northwestern University Medical School, Chicago, Illinois  
11:00-12:15 Histaminic Cephalgia and Migraine  
BAYARD T. HORTON, M.D., Mayo Clinic, Rochester, Minnesota.

P.M.

- 2:00- 3:00 Bronchial Asthma in Infants and Children  
M. MURRAY PESHKIN, M.D., Instructor, College of Physicians and Surgeons, Columbia University.  
3:00- 4:00 Chronic Cor Pulmonale—Complications of Chronic Lung Disease  
MAHLON DELP, M.D., Assistant Professor of Medicine, School of Medicine, University of Kansas.  
4:00- 5:00 Allergic Rhinitis  
FRENCH K. HANSEL, M.D., Associate Professor of Otolaryngology, Washington University.  
5:00- 5:45 Allergic Rhinitis—Management and Treatment  
W. BYRON BLACK, M.D., Kansas City, Missouri

Wednesday, May 7, 1947

A.M.

- 9:00-10:00 Food Allergy  
ORVAL R. WITHERS, M.D., Associate Professor of Medicine,  
School of Medicine, University of Kansas.
- 10:00-11:00 Common Air Molds in Relation to Allergy  
HOMER E. PRINCE, M.D., Associate Professor of Medicine, School  
of Medicine, Baylor University, Houston, Texas
- 11:00-11:30 Poison Ivy  
LAWRENCE J. HALPIN, M.D., Cedar Rapids, Iowa
- 11:30-12:15 Ménière's Disease  
BAYARD T. HORTON, M.D., Mayo Clinic, Rochester, Minnesota

P.M.

- 2:00- 3:00 Antibiotics in Allergy  
EDWARD H. HASHINGER, Professor of Clinical Medicine and Di-  
rector of Graduate School of Medical Education, School of Medi-  
cine, University of Kansas.
- 3:00- 4:00 Skin Allergy Due to Fungi  
CHARLES C. DENNIE, Professor of Dermatology, School of Medi-  
cine, University of Kansas
- 4:00- 5:00 Dermatologic Allergy in Infancy and Early Childhood  
ALBERT STOESEER, M.D., Clinical Professor of Pediatrics, Uni-  
versity of Minnesota, Director of Allergy Clinic at University  
Hospital and Minneapolis General Hospital.
- 5:00- 5:45 Practical Management of Contact Dermatitis  
R. L. SUTTON, JR., M.D., Associate Professor of Dermatology,  
School of Medicine, University of Kansas.
- 7:00-10:30 Dinner and Round-Table Discussion

Thursday, May 8, 1947

A.M.

- 9:00- 9:45 Physical Allergy.  
CECIL KOHN, M.D., Kansas City, Missouri.
- 9:45-10:30 Status Asthmaticus—Treatment  
ALLAN G. CAZORT, M.D., Little Rock, Arkansas
- 10:30-11:00 Pathology of Allergy  
LEON UNGER, M.D., Associate Professor, Department of Medicine,  
Northwestern University Medical School, Chicago, Illinois
- 11:00-11:30 Gastrointestinal Allergy  
ORVAL R. WITHERS, M.D., Associate Professor of Medicine,  
School of Medicine, University of Kansas.
- 11:30-12:15 Value of X-Ray in Allergy—Diagnosis and Treatment  
GALEN M. TICE, Associate Professor of Roentgenology, School of  
Medicine, University of Kansas.

P.M.

- 2:00- 5:45 Laboratory and Clinical Sessions  
Laboratory Session (Technique)—Asthma Clinic—Hay-Fever Clinic—  
Dermatology Clinic

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The fee for the course is \$50.00 payable at the registration desk, University of Kansas Hospital, W. 39th St. and Rainbow Blvd., Kansas City, Kansas. Applications for the course and for hotel reservations should be placed with the chairman of the Program Committee, Orval R. Withers, M.D., 1418 Bryant Building, Kansas City, Missouri. Doctor Withers has made arrangements for hotel reservations at the following three hotels: Bellerive, 214 East Armour; LaSalle Apartment Hotel, 922 Linwood; and Ambassador Hotel, 3560 Broadway. Only twin bedrooms are available.

All physicians interested in Allergy are invited to take this course.

# Progress in Allergy

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## PEDIATRIC ALLERGY

### A Critical Review of Recent Literature

JEROME GLASER, M.D., F.A.C.A.  
Rochester, New York

#### BRONCHIAL ASTHMA

The relationship of the thymus gland to dyspnea in infancy and childhood continues to puzzle pediatricians, and the question cannot yet be regarded as settled. Possibly Carr<sup>10</sup> has made a useful contribution to this subject in reporting a new descriptive term which denotes a disease entity which he states is frequently responsible for strangulation in the young, namely, "status thymico-asthmaticus." Under this heading is presented a series of cases occurring in widely varying age groups, in which death has occurred from asphyxia and in whom the thymus is enlarged. This enlargement is of lesser degree than that seen in patients who have died of acute tracheal compression from an enlarged thymus, and associated with it is a hyperplasia of the lymphoid system which, instead of being generalized, is limited largely to the bronchi and bronchioles. Because the lymphocytic infiltration is in the submucosa and among the muscle fibrils, as well as peribronchial, the term asthmaticus is included. This picture cytologically resembles a developing or existing asthma, and the clinical course is differentiated with difficulty from true asthma, except for the single but very important fact that the status thymico-asthmaticus group shows no beneficial response to the injection of epinephrine. The author states that the pathological picture resembles that described by Waldbott<sup>91</sup> in his report of two infants apparently dying from asthma. Because of the pathological changes, Waldbott stated at that time that he thought it possible that thymic death and death from allergic shock might be equivalent.

Flensburg<sup>30</sup> has attempted to discover the chances for recovery from bronchial asthma in infancy when treated by the usual measures employed in Denmark previous to the introduction of specific therapy in 1943. The study was made on the basis of satisfactory replies to 298 questionnaires. Of these, there were 190 boys and 108 girls. In the great majority, 197 out of 298, the attacks commenced before the age of five years. The usual ages of onset were the second and third years. The asthma was regarded as having ceased in those patients who had no attacks for at least one year. In most of the boys the asthma ceased between twelve and fifteen years of age. With the girls the attacks usually ceased between nine and twelve years.

Among the 298 children were 100 who constantly suffered from attacks and who, at the time of the inquiry, were more than fifteen years old, besides sixteen children whose attacks of asthma had ceased after the age of fifteen. Of these 116 patients, thirty-nine, or about a third, reported that they had chosen a special profession on account of their asthma. About 40 per cent of the cases of asthma starting in infancy recovered spontaneously or under the treatment employed. Infantile asthma occurred much more frequently in boys than in girls. Of the 298 children, school attendance was seriously interfered with in 139, or almost half of the cases. Among

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Chief of the Pediatric Allergy Clinic of the Strong Memorial and Municipal Hospitals of the University of Rochester School of Medicine and Dentistry, and chief of the Allergy Clinic of the Genesee Hospital; Rochester, New York.

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116 children whose attacks had ceased at the time of inquiry the average duration of the disease had been 7.4 years. In the case of the boys, the average was 7.7 years; for the girls, 6.9 years.

The following explanations were given in the questionnaires as probable causes of cessation of the asthma:

Patient's removal to another place in the country, or another residence in the same town.....	31
No attacks since patient's discharge from hospital.....	10
Sanitation of lodgings or room.....	9
Spray treatment .....	3
Residence at health resort or sanatorium for children.....	2
Sport and open air environment.....	2
Dietary treatment .....	2
Corset treatment .....	2
Respiratory gymnastics .....	1
Vaccination against "colds".....	1
Attacks ceased after whooping cough.....	1
Attacks ceased after rheumatic fever.....	1
No cause known.....	49
No information .....	6
Total .....	120

Melamed<sup>57</sup> has contributed some interesting statistical figures on the occurrence of bronchial asthma in children in Palestine. The difficulty of securing such statistics is the same in Palestine as it is elsewhere, consisting chiefly of (1) the lack of a central institution to which all cases of bronchial asthma are reported, (2) the lack of long-continued observations in individual cases, and (3) the difficulties of diagnosis, particularly at the onset of bronchial asthma in childhood. Confusion is also caused by the fact that some authorities consider asthmatic bronchitis as a form of bronchial asthma. For statistical purposes, the author attempted to differentiate between these two conditions. The author's material consisted of the children in the Sick Fund of the southeastern district of Tel-Aviv for the year beginning July 1, 1943. The Sick Fund numbered 1,400 children the first year of the study. The number of asthmatic children under seven years of age at that time was sixty-nine. Of these, twenty-three had bronchial asthma and forty-six had asthmatic bronchitis. In the second year of the study, which began July 1, 1944, there were 1,600 children. Of these, among the children seven years of age or less there were 105 with asthma; thirty-seven had bronchial asthma, and sixty-eight had asthmatic bronchitis. The average percentages of children in the two groups, 5 per cent for the first year of the study and 6.5 per cent for the second year of the study, are quite close. It is interesting that in the total series, the sex distribution (50.5 per cent for females and 49.5 per cent for males) was almost identical. This is not in accordance with the figures presented above by Flensburg<sup>30</sup> from Denmark or the previously published figures by Bray<sup>6</sup> from England, both of which showed a marked preponderance of asthma in boys. It is interesting that about twice as many cases of asthma occurred in children with fair complexions (66 per cent) as in dark-skinned children (34 per cent). The average onset of the asthma was between four and six years of age. The majority of the asthmatic attacks occurred during September, October, and November. The month with the least number of attacks was August.

### COMPLICATIONS OF BRONCHIAL ASTHMA

A case of probable death from asthma was reported from the Children's Memorial Hospital in Chicago.<sup>12</sup> The child, a boy twenty-two months of age, was first seen at the age of eleven months because of asthmatic bronchitis which followed an upper respiratory tract infection at the age of eight and one-half months.



A running nose and intermittent cough had persisted since the initial attack. The child was relieved after a few days of symptomatic treatment and was readmitted to the hospital a month later for bronchoscopy. The findings were normal. At the age of fifteen months, bronchial asthma was diagnosed and he was studied with negative results. The child was then taken to Alabama, where his condition remained unchanged, and he received numerous injections of adrenalin without relief. He was restudied from the standpoint of bronchial asthma by the same allergist (Dr. Leon Unger) at the age of eighteen months, again with negative results.

The boy's final admission was at the age of twenty-two months. Two days before admission he had had a running nose and on the day before, severe asthmatic attacks had started. Adrenalin had been given repeatedly without relief. The only other medication the child had received had been atropine drops three times a week for strabismus. The child was cyanotic and comatose on admission and critically ill. His rectal temperature was 100.6°. There were numerous wheezes and rhonchi over both lungs. A roentgenogram of the chest was normal. He responded rather well to parenteral aminophyllin, adrenalin in oil, and oxygen. That night he again became worse, and in spite of a variety of therapeutic measures, including parenteral fluids, penicillin and coramine, his temperature rose to 107.2° F. and dropped to 101.6° F. three hours later, the patient dying shortly thereafter.

At autopsy, 100 to 150 c.c. of sterile fluid of unknown origin was found in each pleural cavity. The branches of the bronchial tree were entirely occluded with a thick, light-green, tenacious mucus which by smear showed numerous eosinophil cells. On culture, *B. coli* was isolated. The final anatomical diagnosis was marked mucopurulent bronchitis and bronchiolitis; asthma (clinical); bilateral hemothorax; foci of atelectasis; and compensatory emphysema; foci of pulmonary edema. As Unger suggested in discussion of this case, the child might possibly have been helped by bronchoscopy in his terminal illness, but his condition was considered too critical to attempt this.

A death from asthma in a thirteen-year-old boy has been reported by Pedrera.<sup>62</sup> The onset of the attack was sudden and severe. He did not respond to therapy and died a few hours after the onset. There was no necropsy. The family history was positive for allergy, in that the father was known to be sensitive to fish and a younger brother had died of anaphylactic shock following the administration of tetanus antitoxin. The present patient's asthma had started at the age of six years and had gradually increased in severity. At the age of twelve years, he was studied from the allergic standpoint and did very well on the therapy instituted. After he had been free from attacks for two months, he was not seen again until his terminal illness. The author briefly discusses the mechanism of death from asthma which he regards as not yet having been satisfactorily explained. He believes that dehydration and disturbances of acid-base equilibrium may play a large part.

A case of mediastinal and subcutaneous emphysema was described in an asthmatic girl, five years of age, at the Children's Memorial Hospital of Chicago.<sup>11</sup> She had been referred with a diagnosis of virus pneumonia because of the numerous râles which had been heard on auscultation of the chest. On more complete physical examination and x-ray investigation, the true diagnosis was discovered. The child made an uneventful recovery. In the discussion, the subject of emphysema of this nature is beautifully reviewed. The characteristic x-ray finding in mediastinal emphysema is the elevation of the mediastinal pleura from the mediastinum and pericardium, producing a rather characteristic and unique line on one or both sides of the mediastinal shadow.

On the left, this line is commonly visible above the pulmonary vessels. The condition is produced by the escape of air from ruptured alevoli. This travels along the course of the vessels into the mediastinum. The most persistent finding is a crunch-

ing, bubbling sound heard over the precordium during the cardiac contractions. This is sometimes mistaken for air in the pericardial cavity. Since cardiac tamponade with subsequent death may result from the increased mediastinal pressure due to mediastinal emphysema, it is occasionally necessary to release the air in the mediastinum surgically. This may be done by needle puncture, dissection through the neck, or splitting the sternum.

Pneumothorax may occasionally be produced by the rupture of an overdistended mediastinal wall, rather than by a pleural defect or a ruptured emphysematous bleb. Subcutaneous emphysema as a result of bronchial asthma in children is not common, only seven cases having been reported up to 1941 in children under ten years of age.

Derbes and Engelhardt<sup>19</sup> have summarized their studies, previously reviewed in these columns,<sup>34</sup> on the influence of bronchial asthma on the heart in childhood, with the statement that their varied data tends to show that in children uncomplicated bronchial asthma is not a factor in the production of heart disease.

#### CONDITIONS SIMULATING BRONCHIAL ASTHMA

Acute and chronic respiratory disturbances in which the clinical manifestation is an expiratory type of dyspnea associated with a generalized emphysema, are not uncommon during the first few years of life. This fact is discussed by Nelson and Smith.<sup>58</sup> Respiratory obstruction in these instances is mostly in the distal or smaller bronchioles, and, clinically, such diagnostic terms are employed as bronchiolitis, capillary bronchitis, pneumonitis, interstitial pneumonia, and sometimes aspiration pneumonia. There is usually both inspiratory and expiratory obstruction but the difficulty in expiring the air is more prominent, and air is trapped in the alveoli, producing emphysema. Clinically, there are certain similarities to asthma, but in contrast to the usual relatively short duration and self-limited course of the average attack of asthma, even the acute forms of obstructive emphysema in infants tend to persist for a week or so and often much longer. Furthermore, while asthma is perhaps the most frequent cause of obstructive emphysema in older children, it is relatively uncommon in the first year or two of life when the conditions discussed characteristically occur. Producing this type of respiratory disturbance, the authors give illustrative cases including aspiration of amniotic fluid during birth, cystic fibrosis of the pancreas, atypical bronchopneumonia, laryngotracheobronchitis, milary tuberculosis, aspiration of zinc stearate powder, and chronic passive congestion secondary to congenital heart disease.

One of the above conditions, bronchiolitis, in infants is discussed by Pratt<sup>65</sup> in considerable detail. As other terms for this condition, he mentions bronchitis, capillary bronchitis, asthmatic bronchitis, and bronchopneumonia. Acute bronchiolitis occurs most frequently in infants three to eighteen months of age. It is a syndrome characterized by rapid, labored respiration, audible wheezing, prostration, cyanosis, pulmonary emphysema, and signs of exudate in the smaller air passages, leading to obstructive dyspnea and terminal asphyxiation. It generally begins with nasal discharge followed by a slight cough and an increased respiratory rate. The breathing becomes noisy and is described as "wheezing" or "rattling in the chest." It may be accompanied by diarrhea or vomiting, and there is usually moderate fever. As the condition becomes worse, breathing becomes more difficult and there is often audible wheezing. This occurs in about one-third of the subjects and is a symptom which leads to confusion of this condition with bronchial asthma. Pratt makes the interesting observation that allergy or chronic respiratory tract infection is not more frequent than normal in the families of these patients. However, he does not mention eosinophil smears of the nasal or pharyngeal mucus, and there is no mention of blood counts with reference to eosinophilia.

As the condition progresses, the character of the respirations becomes distinctive. The symptoms are those of obstructive emphysema. The accessory muscles of

respiration are used; the thoracic cage is fixed in a position of inspiration. The chest is hyperresonant to percussion; the breath sounds during expiration are moderately prolonged. Wheezing may be heard on auscultation of the chest in about half the cases. The most distinctive feature on auscultation is the presence of many râles throughout the lungs. The breath sounds vary considerably in character and may resemble bronchial asthma. The roentgenograms show certain characteristic changes<sup>60</sup>: emphysema involving all portions of the lungs; bulging of the emphysematous tissue into the interspaces is a prominent feature. There is increase in bronchovesicular markings and varying degrees of peribronchial infiltration, with small patches of pneumonic consolidation or atelectasis toward the base. There is irregularity of aeration with multiple small areas of emphysema surrounded by normal or partially atelectatic lung tissue. The mediastinum is not displaced. The diaphragm is depressed and the thoracic cage is fixed in the position of extreme inspiration.

A small proportion of the infants, although seriously ill, make a rapid recovery within a day or two. Only rarely does acute bronchiolitis progress into a protracted bronchopneumonia. Such an occurrence should lead one to suspect the presence of some underlying disturbance, such as pancreatic fibrosis or the aspiration of a foreign body.

The treatment of the disease is with measures appropriate for an acute pulmonary infection. Sulfadiazine is recommended. Cool, moist air with a relative humidity of 95 to 100 per cent is said to be better than steam. For difficult breathing, aminophyllin in doses of .006 grams per kilogram (1/20 of a grain per pound), combined with 2 c.c. per kilogram (1 c.c. per lb.) of a 50 per cent dextrose solution, is given slowly intravenously. This is repeated every six to eight hours if effective. It should be discontinued if there is any tendency towards thickening of the secretions. Oxygen is useful, and the author recommends a nasal catheter or an open top box with cool moist air. For circulatory collapse, caffeine sodium benzoate in doses of 0.03 to 0.13 grams (1/2 to 2 grains), or metrazol, 0.25 or 0.5 c.c. (4 to 8 minims), can be used. For abdominal distention, pitressin, 0.5 to 1.5 units, is given intramuscularly, or prostigmin methylsulphate, 0.25 to 1 c.c. of a 1:4000 solution, intramuscularly or subcutaneously.

Adenoid bronch sinusitis in infants and children is described by Clifford, Neuhauser, and Ferguson.<sup>14</sup> This develops commonly as a complication of an upper respiratory infection. The history is that the patient has never fully recovered from an original "cold" acquired some months previously. The infected adenoid tissue and nasal sinuses produce a purulent discharge which obstructs the nasal passages and descends into the trachea and bronchi. In time, this postnasal dripping may penetrate the finer bronchi and cause profuse peribronchial infection. The main symptoms are persistent nasal discharge, mouth breathing, snoring at night, postnasal drip at night causing cough, and profuse nasal discharge during the day. An attack of asthma may be precipitated, or the disease may be complicated by capillary bronchitis or pneumonia.

Adenoid bronch sinusitis is characterized by periods of exacerbations and remissions. Recurrent attacks of tonsillitis, cervical adenitis and otitis media are frequent. Nearly all cases begin in September, October, or November. The patients range in age between eleven months and eight years. It is rarely seen at later ages because of the development of individual immunity, the relative increase in size of the nasal pharynx, and atrophy of lymphoid tissue, which generally takes place in adolescence. The author states that good results are obtained by a combination of chemotherapy and surgery. Although this condition is often seen in children known to be allergic, the authors do not discuss the relationship between allergy and this disease.

A condition closely related to the above has been described by Dutton and

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Fuchlow<sup>23</sup> under the term of the "sinobronchial syndrome," which may be defined as an involvement of the sinus membranes by an infectious process of sufficient intensity to have implanted itself secondarily upon the bronchial mucous membranes by virtue of postnasal drainage. Admittedly, there may be considerable difficulty in differentiating sinus involvement due to such a chronic infection from that due to allergy. The sinobronchial syndrome may be identified as at least one factor in the production of otherwise unexplained symptoms in children apparently under adequate allergic management and for which no atopic etiology is demonstrable. The authors summarize the differential diagnosis between asthma due to atopy and asthma due to the sinobronchial syndrome as follows:

### DIFFERENTIAL DIAGNOSIS

	<i>Asthma Due to Atopy</i>	<i>Asthma Due to Sinobronchial Syndrome</i>
1. Onset	Eczema, hay fever, asthma triad	Asthma begins with colds
2. Duration of attacks	Paroxysmal, short duration	Gradually developing, longer duration
3. Fever	Not usual	Usual
4. Response to adrenalin	Good	Poor
5. Leukocytosis	Infrequent	Frequent—moderate to high
6. Sedimentation	Very slow	Normal or rapid
7. Nasal smears	Eosinophilic	Neutrophilic
8. Bacteriology	Indifferent	Usually streptococcal pneumonia or staphylococcal
9. X-ray chest	Minimal changes	Striking changes
10. X-ray sinuses	Minimal changes	Striking changes
11. Seasonal incidence	Not seasonal or corresponds to pollen season	Winter or change of weather

The symptoms of the sinobronchial syndrome as they occur in the allergic individual are generally rhinitis, postnasal drainage, cough, wheezing, and fever. The physical findings are not strikingly different than those found in atopic asthma. Roentgen treatment is recommended and this is best carried out in the chronic phase. Generally, about 400 roentgens over the sinuses and 800 to 1,400 over the chest, in four to six daily treatments, are given. There is generally a gradual improvement of the entire condition of the patient within four to six weeks, an improvement which persists for a variable period of time up to several months or even indefinitely.

While bronchial stenosis due to syphilis has been described and the same condition caused by tuberculosis has received considerable attention, little has been written about nontuberculous bronchial stenosis. Hollinger<sup>43</sup> demonstrated in 1938\* that bronchial inflammation can cause bronchostenosis and finally bronchiectasis. This disease has recently been reviewed by Schmidt.<sup>75</sup> It is characterized by a cyclic course. The attacks usually start with an irritating nonproductive cough. Chills and fever, 38.8° C. to 39.4° C. (102° F. to 103° F.), and general malaise occur, and this episode lasts on the average from two to seven days. Then, variable amounts of sputum, occasionally blood tinged, are coughed up and the symptoms are relieved. Symptom-free periods may last from three months to three years. These individuals generally have a history of antecedent pneumonia, severe tracheobronchitis, or repeated attacks of asthmatic bronchitis. Recurrent pneumonia, influenza, malaria, and brucellosis are some of the diseases commonly considered in a differential diagnosis. The attacks are due to stagnation of infected material distal to a stenosed bronchus. A local pneumonic process develops. Symptoms persist until drainage is re-established.

Bronchoscopy is the only clinical method of determining whether or not bronchial stenosis exists and is the only way in which such a lesion can be satisfactorily treated. It is wise, however, to wait two or three weeks after recovery before

attempting treatment by this procedure if there has been a recent attack. The author reviews twenty-five cases, in fifteen of which the bronchial stenosis was secondary to asthma or asthmatic bronchitis. There were a number of children in the series, the youngest of whom was six years of age. Bronchoscopic dilation produces satisfactory results in about 66 per cent of cases. In a certain number of cases the stenosis recurs and it is necessary to repeat bronchoscopic dilation. The physical and roentgenographic findings vary. In some cases, they may indicate partial atelectasis of the lower lobe of one lung although the disease may occur in the upper lobes or in the middle lobe of the right lung. In other cases, the above findings may be negative.

Apparently a very similar, if not identical, condition has been described by Leegaard<sup>50</sup> in Sweden, under the name "nonspecific circumscribed bronchitis." He states that the cause of condition must be (if it is really a distinct disorder) an ordinary acute, diffuse infection of the lower air passages. It is then reasonable to suppose that on a mucous membrane thus altered by inflammation there may arise more pronounced changes or an erosion, occasioned by traumatization of the diseased membrane and occurring perhaps most readily during severe coughing, or possibly due to irritation by a very minute foreign body which is afterwards removed by coughing or in some other manner. The condition probably arises frequently and is called a cold or pulmonary catarrh, and most frequently subsides spontaneously without leaving any sequelae. Acute and chronic lung diseases frequently give rise to similar bronchial changes. The most important symptoms are cough, hemoptasis, and signs of bronchial stenosis. Circumscribed lesions of the mucous membrane of the larger bronchi, with redness, edema, and considerable granulation tissue, were demonstrated on bronchoscopy. In two patients there was atelectasis of one lobe. In the majority of cases the disease subsides spontaneously, but considerable secondary changes may occasionally be produced in the lungs and bronchiectasis may result. The author describes six cases, four in women between the ages of twenty-nine and forty-one, one case in a man aged twenty-five, and another in a boy seven years of age.

Diaz-Nielson<sup>20</sup> has reported a case of bronchiectasis in a six-year-old boy who had been ill since the age of three years, following what was diagnosed as pneumonia. Since then, he had had almost constant cough with expectoration. The roentgenogram suggested a diagnosis of bronchiectasis. This diagnosis was confirmed by bronchography. The author believes that bronchiectasis from any cause is commonly associated with a constitutional predisposition. Although an attempt should always be made to treat the condition medically, it is potentially a surgical disease. If treated surgically, radical measures are generally advisable and are commonly successful. Lobectomy or pneumonectomy are the operations of choice but these have a mortality of 10 per cent.

## BRONCHOSCOPY IN ALLERGIC PULMONARY DISEASE

It is often not realized that bronchial asthma is but one of many forms of obstructive emphysema, although it is indeed the commonest form. The differential diagnosis of bronchial asthma thus becomes a question of determining from which type of obstructive emphysema a patient is suffering. Holinger and Rigby<sup>44</sup> have discussed the question of bronchial obstruction in infants and children in considerable detail. The four types of valvular obstruction in bronchial asthma—by-pass, click, stop, and ball—are described. The important symptoms of bronchial obstruction, while not completely characteristic, are fairly constant. These are: cough, which may be dry and nonproductive for weeks and then suddenly be associated with hemoptasis and a foul, purulent sputum produced by superimposed infection; wheeze, commonly heard throughout the chest and loudest over the location of the obstruction; dyspnea of varying degree. Pain is not common but occasionally occurs and may be localized by the patient to the site of the foreign body.

One of the most constant physical signs in almost all cases of bronchial obstruction is the definite limitation of motion on the involved side, independent of the degree of obstruction. Tracheal obstructions due to mediastinal neoplasms not infrequently involve the esophagus as well, and consequently the child has difficulty in swallowing and regurgitates food into the trachea due to esophageal overflow. The increased positive pressure of expiration has no appreciable effect on blood flow through the thorax. However, the increased negative pressure on inspiration has definitely harmful effects, resulting in pulmonary congestion, transudation, and edema.

In summary, the authors state that physiological effects of tracheobronchial obstruction may be divided into their respiratory and cardiovascular reactions. Mild obstruction results in a dyspnea which remains compensated by reflex and physiochemical stimulation. Severe obstruction results in respiratory decompensation or anoxia. Long-standing obstruction results in pulmonary suppuration, bronchial obstruction, and bronchiectasis. The cardiovascular phenomena manifest themselves by pulmonary edema and finally circulatory failure due to rising intrathoracic negative pressures.

Lell,<sup>52</sup> in an exceedingly valuable bronchoscopic study of 176 children thought to be suffering from epinephrine-fast bronchial asthma, has pointed out the great value of the bronchoscope in the diagnosis and treatment of this condition. Of these patients, 130 were found to have true bronchial asthma; thirteen had a foreign body in the bronchus; in fourteen there was tracheal compression from external causes; eight had organic changes in the larynx; five had foreign bodies in the esophagus; five others had foreign bodies in the larynx; and one had a retropharyngeal abscess. Lell states that all patients examined during an attack of asthma showed changes which are fairly constant and uniform. The mucous membrane is always hemorrhagic, red, and redundant, greatly reducing the caliber of the lumen of the trachea and both main bronchi. Secretions are always present and so tenacious that they are difficult to aspirate. The classic phenomenon of collapse of the posterior tracheal wall is frequently present in children and almost always present in adults during status asthmaticus.

It is of great importance that a hypodermic injection of epinephrine be made just before bronchoscopy; the intravenous injection of aminophyllin produces the same effect. These procedures appear to cause the mucus to come out into the bronchi and trachea. In all cases, during the bronchoscopic examination, oxygen was administered through an attachment on the bronchoscope, thereby relieving the dyspnea. Lell emphasized the fact that treatment should be given as soon as possible during an attack.

Dighiero<sup>21</sup> has discussed the importance of bronchoscopy in the diagnosis and treatment of bronchial asthma on the basis of a study of twenty children, sixteen of whom were observed in the intervals between attacks of asthma and four during attacks. Those examined between attacks comprised three groups. In the first group, no pathological changes were visible. The mucosa was normal and there were no appreciable secretions or alterations. In the second group, there was severe congestion of the tracheal and bronchial mucosa with hypersecretion, a condition often called "allergic mucosa." The patients with these lesions of the bronchial mucosa were also sufferers from allergic rhinitis and had personal and family histories of allergy. The third group showed changes resembling chronic tracheobronchitis. The mucosa was thickened, pale, dull and covered with mucopurulent secretion. There were also bronchial changes characterized by flaccidity, loss of elasticity, and limitation of the movements of expansion and contraction. This flaccid state creates a favorable condition for emphysema.

The differential diagnosis between asthma complicated by bronchial infection and chronic tracheobronchitis with attacks of asthmatic dyspnea, can be made only by the

clinical history. In such cases it is necessary to treat the bronchial infection. The author has had good results from repeated bronchial aspirations, bronchoscopic instillation of sulfonamides, topical applications, et cetera, and, in cases where there was no great obstruction, from pulmonary nebulization with sulfonamides or iodized oil. In addition to these local measures, he advises general symptomatic treatment and such specific measures as may be necessary after the patient has been studied from the allergic standpoint. Bronchial aspiration combined with bronchial insufflation of oxygen is an emergency treatment in all cases of serious asthmatic attacks, with asphyxia and cyanosis, in which other treatment has failed.

Only four patients were studied during attacks. In all cases there was congestion and edema of the mucosa. The congestion was not equal in all instances, being more accentuated in those patients in whom the mucosal congestion was of an allergic nature. These lesions were accompanied by thick, mucoid or mucopurulent viscous secretions. There were also changes in the tracheobronchial movements, varying with the degree of dyspnea and the tonicity of the bronchial walls. Bronchoscopically, bronchial spasm was not seen, although it has been noted by others. The changes that were actually observed were sufficient to explain the dyspnea and the difficult breathing characteristic of asthmatics.

When congestive lesions of the mucosa as seen in allergic asthma prevail, the attacks start suddenly and rapidly become severe but always yield readily to epinephrine. On the other hand, when there is bronchial infection and changes in the tone and elasticity of the bronchi, the attacks are milder but much more prolonged; they respond very little, if at all, to epinephrine, and between attacks the patient is subject to wheezing, especially at night. A permanent form of asthmatic breathing finally develops.

### TREATMENT OF BRONCHIAL ASTHMA

A discussion offering many practical suggestions in the management of asthmatic children has been presented by Bowen.<sup>4</sup> The use of the usual routine measures in the case of such children is thoroughly discussed. The uselessness of the routine removal of the tonsils and adenoids as a cure-all for nasal allergy and asthma is emphasized. In discussing the role of foods, Bowen makes the statement that he had never seen a proved case of allergy due to cane sugar. For the use of children who may be sensitive to various forms of cod liver oil, the use of Provatal (Wyeth) is recommended. In this preparation, vitamin A is supplied by carotene and vitamin D by irradiated ergosterol which is not derived from a fish source. The preparation is put up in a sesame oil base. In his experience, hyposensitization to food by hypodermic injection is a method which is not free from danger and as a routine procedure is to be condemned. Caution in the interpretation of skin tests is emphasized, and it is pointed out that tests with food give reliable information in less than 40 per cent of cases. Animal pets with fur or feathers are not to be recommended, regardless of the skin tests.

In taking the history, inquiry should be made regarding a child's hobbies. Bowen reports two cases of children who developed asthma while arranging their stamps in books. In each case LePage's glue was suspected and this was confirmed by further testing. This glue has a fish base. The adhesive on United States postage stamps is said to have a vegetable base. Glue is also used in the making of kites and model airplanes. In warning against cosmetics, it is pointed out that many of these not only contain orris root but also various cereal flours as rice, wheat, oatmeal, and corn. The importance of inquiring as to the use of previous medications, especially proprietary preparations, is discussed. These medications often contain aspirin, quinine, phenolphthalin, iodine, or arsenic.

In this communication Bowen introduces the very useful term "wet sleeper." He describes the child whose forehead is always beaded with sweat shortly after retiring and whose pajama neck is wet. At times, the perspiration may be of such

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degree that one wonders about nutritional imbalance or evidence of disease. Bowen states that it is this type of child who tolerates ephedrine poorly and may present the disagreeable side reactions of this drug. To avoid this he recommends the use of propadrine hydrochloride since its action is chiefly peripheral and does not have as many side reactions as ephedrine. Campbell<sup>9</sup> also some years ago pointed out that the allergic child is often prone to excessive perspiration. While I have not made a statistical study of this subject, from my experience in the general practice of pediatrics, I am inclined to feel that excessive perspiration is just one phase in the development of vasomotor stability as a child grows older. Generally speaking, the allergic child has less vasomotor stability than the nonallergic child and would, therefore, be expected to perspire with less provocation.

In treating with epinephrine, warning is given against using an unnecessarily large dose. In administering epinephrine in oil, one should be sure that the patient is not allergic to the preparation from which the oil base is made, as sesame oil or peanut oil. Gelatin is also sometimes used, and allergy to this may be present. Bowen has found the inhalation of 1:100 epinephrine of little value in children under six years of age. If this preparation is used, it is important that the patient be instructed to rinse the mouth in order to minimize throat dryness and gastric distress. If epinephrine by injection is used, Bowen makes the practical point that it is much less expensive for the parent to buy an ounce of this in a rubber-stoppered bottle than to obtain the preparation in ampules. Aminophyllin may be administered intravenously in children in doses of 0.24 to 0.48 grams (3-3/4 to 7½ grains) in 10 to 20 c.c. of distilled water. This should be administered very slowly over a period of ten minutes. According to Bowen, morphine should never be used in asthma.

It is important that allergic children be early immunized against diphtheria, pertussis, and tetanus. The child should also be vaccinated against smallpox if possible before he is a year of age. The question arose as to whether a vaccine prepared from virus grown in egg (chorioallantoic membrane) could be safely used in a child known to be egg sensitive. In order to discover the answer to this question, Bowen vaccinated five children who were completely intolerant to egg with such a vaccine. Four had successful takes and none of the five showed any unusual reaction. He concludes, therefore, that such material may be used routinely in vaccinating egg-sensitive children. This is true even though it has been shown that this vaccine does contain some egg protein. The reviewer would like to point out that in vaccination against smallpox, the vaccine is not commonly injected. For the prophylaxis of those conditions (yellow fever, typhus, influenza) where it is necessary to inject a vaccine-containing egg, very severe reactions may result in egg-sensitive individuals.

Bowen believes that vaccine therapy has a definite place in the treatment of certain asthmatic children. To this group belongs the child who rarely has asthma unless he has an upper respiratory infection. Bowen has found that a good stock vaccine is as satisfactory as an autogenous vaccine. Annual booster injections of pertussis vaccine should be encouraged.

As a complication of treatment by the injection of epinephrine in oil, Ratner<sup>68</sup> describes the case of a boy four years of age who was given 1 c.c. of Parke-Davis adrenalin in oil, the base of which is peanut oil, into the buttocks by another physician. The area of injection remained indurated and gradually over a period of three months the indurated area spread and fluctuant areas developed. The affected region was dull red in color, measuring about 7 centimeters in diameter. Infection was suspected but oleoma was diagnosed. This was removed surgically. The material showed fat globules microscopically. Oleomas, once formed, have a tendency to enlarge slowly and then gradually break down. In this particular case, Ratner<sup>†</sup> states that the boy was not sensitive to peanut oil.

<sup>†</sup> Personal communication to the author.



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Prigal, Fuchs, and Schulman<sup>67</sup> have discussed the treatment of bronchial asthma with rectal suppositories of aminophyllin and sodium pentobarbital. The work was done in a clinic with ambulatory patients, who as a rule do not have severe asthma. The series, in addition to adults, included five children ranging in age from two to thirteen years. The results were just as good in children as in adults, perhaps better. Possibly this was due to the relatively large doses as compared with those given to adults. The dose for children was 0.25 grams of aminophyllin and 0.5 grams of pentobarbital sodium. The authors point out the obvious advantages of the rectal administration of aminophyllin in children as compared with intravenous administration. It was found that when the sodium pentobarbital was added to the aminophyllin suppository it required about one-half the time to secure the therapeutic effect as when aminophyllin was used alone. The addition of a barbiturate to aminophyllin suppositories to assist their action was described by the reviewer in the first of these communications.<sup>33</sup>

The authors observed that occasionally following the use of suppositories the patients complained of slight itching or burning, or cramps, or diarrhea. They state that this is due to failure to insert the suppository high enough into the rectum and that much of the difficulty may be overcome by lubricating the suppository with an anesthetic ointment. However, in my personal experience with aminophyllin suppositories, I have found that occasionally nausea and vomiting will occur from the suppositories regardless of how they are administered, and this probably represents a central reaction to the drug.

Lee,<sup>40</sup> in a general review of the subject of allergy in pediatrics, states that she has seen several sterile abscesses following the supposedly intramuscular injection of aminophyllin. When given too rapidly or in too large amounts intravenously, aminophyllin has produced profound shock, necessitating intravenous fluids and cardiorespiratory stimulation.

In connection with any discussion of the use of aminophyllin in childhood, the reviewer would like to point out that the limits of tolerance for adults and children with this drug have not yet been established. However, it is quite evident from clinical experience that the doses necessary to procure a favorable therapeutic effect are considerably less than what may possibly be the toxic doses.

Prigal<sup>66</sup> has also developed what may prove to be an exceedingly valuable addition to the armamentarium of the pediatric allergist in the treatment of bronchial asthma and pulmonary infections. He has devised an apparatus by means of which various solutions of drugs may be converted into aerosols by means of the passage of a current of steam. The apparatus used is very similar in construction to some of the devices now on the market for producing steam for croup tents. By means of this apparatus he has successfully treated asthma by aminophyllin aerosol. Prigal states that other drugs such as penicillin solutions, solutions of sulfonamides, and ammonium chloride may be converted into aerosols without loss of potency by the same method.

Under the medical supervision of Dr. M. Murray Peshkin, a project has been developed at the National Home for Jewish Children at Denver which will eventually yield much valuable information regarding the effect of climate on asthmatic children, our knowledge of which is pathetically meager.<sup>56</sup> For the past five years, this Home has been caring for underprivileged children suffering from acute bronchial asthma and other refractory upper respiratory diseases. The Home is located in Denver and is available to children whose families cannot afford expensive and costly private care. The children remain until the physician recommends that they be returned to their homes. In a comparatively normal environment and sharing the companionship with other children, the asthmatic child is cared for by a staff trained in child welfare and under the direct medical supervision of Dr. Harry I. Goldman.

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During the child's stay at the Home, periodic examinations are made and full reports given to the referring physician and hospital clinics. The Home has a modern, well-equipped infirmary where children requiring bed care are attended by registered nurses under the supervision of the attending physician. The children are housed in attractively furnished congregate-cottages with individual bedrooms. Food of the highest quality is carefully prepared in modern kitchens and special diets are given when prescribed. The children participate in community life by attending the local schools and taking part in communal recreations. In addition to studies made during the child's stay in the Home, an equally thorough after-care program is carried out.

The circumstances of the development of this Home render its present use available only to children of the Hebrew faith. It is hoped, however, that experience gained at the Home will furnish adequate data as to whether or not it is worth while for such homes to be established in suitable areas to which any children who need such care may be sent. Should studies at the Home prove this to be desirable, then data will be at hand which will enable the establishment of such institutions to be made in the most efficient manner.

### RADIATION TREATMENT OF LYMPHOID TISSUE OF THE UPPER RESPIRATORY TRACT

As is well known, primary infections of the lymphoid tissue in the pharynx, especially the nasal pharynx, may extend to the sinuses, ears, larynx, bronchi, and lungs. This is especially true in children, as was emphasized by Crowe.<sup>15</sup> Infection here results in hyperplasia and hypertrophy of lymphoid tissue. Even after adequate removal of the tonsils and adenoids, if infections continue to recur, the posterior and lateral walls of the pharynx become studded with nodules of lymphoid tissue, a condition commonly described as "granular pharyngitis." Nasopharyngoscopy will often show the same condition more frequently and in a more advanced stage in the nasopharynx. Because, in this region, lymphoid tissue is an integral part of the mucous membrane, it cannot possibly be removed entirely unless the entire thickness of mucous membrane is taken out, which of course is impossible. The recurrence, therefore, of adenoid tissue in the nasopharynx is not due to previous faulty surgery but is the normal physiological reaction. The treatment for the recurrence is not a second operation, but irradiation. For this purpose Crowe<sup>16</sup> advises radon, which he has been using for the past seventeen years. This is especially valuable in treating recurrences of lymphadenoid tissue which may block the internal ostia of the Eustachian tubes and thus cause impairment in hearing.

Next to the sex cells, the lymphocytes are the most sensitive cells in the body to beta and gamma irradiation. Therefore, in treating these patients, the dosage employed is so small that there is no danger of a burn or a dry nasopharynx. Under irradiation treatment, the lymphoid mass gradually shrinks and finally disappears, leaving a smooth mucus membrane not unlike that of the nasal septum. This method of treatment, Crowe points out, is of the utmost value in treating children who have recurrent upper respiratory infections which are apparently due to recurrent or persistent infection of the follicles of lymphadenoid tissue in the pharynx which have not been removed surgically and which are not amenable to surgical treatment.

More recently, instead of using radon for such treatment, the tendency has been to use the roentgen ray. Swihart<sup>16</sup> reports a series of ten cases in children ranging in age from four to thirteen years, in whom repeated upper respiratory infections, often accompanied by tonsillitis and occasionally hearing impairment, were treated by the roentgen therapy of hypertrophied lymphadenoid tissue in the nasal and oral pharynx with strikingly good results. Many of these children had not been helped by tonsillectomy and adenoidectomy.

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### ATOPIC DERMATITIS

Robinson<sup>71</sup> has reported on a group of children with eczema from both clinic and private practice. There were 426 cases in the clinic group. About one-quarter of these improved and remained in a satisfactory condition with only local treatment. The results of hospitalization were uniformly good. Of the nonhospitalized dispensary patients who did not readily improve under local treatment, the results were consistently poor. There were 168 private patients. In eighteen, the eruption began a few days after birth; in ten, at one month of age; in twenty, at two months; in ten, at three months; in twelve, at four months; in forty-eight, at five months to one year; in twenty-six, in one to two years; and in twenty-three, between the ages of two and six years. Of these patients, thirty-two did not improve satisfactorily on home treatment and went elsewhere. The others improved either at home or in the hospital.

Robinson employs all means of treatment: environmental control, dietary, and local. His article contains a good historical review of the subject. Environmental control is emphasized. He states that the child should be handled as little as possible, preferably only when a change of diapers is needed. If the child is held, the holder should not use nail polish, perfume, or perfumed powders, and preferably should not wear silk, wool, furs, or rayon. He finds that, in his experience, compound resorcinol ointment has occasionally succeeded when all other medication has failed. It was necessary in some instances to use mechanical restraining devices after hospitalization before improvement could be noted. In Robinson's opinion, these patients had developed a habit itch.

Another general review of the subject has been published by Brain.<sup>5</sup> He states that in dermatological experience infants are rarely allergic to specific foods. This is a statement which is constantly made by dermatologists. I believe it is due to the fact that dermatologists rarely see infants at the early age at which they are seen by pediatricians or pediatric allergists. By the time they get to see the dermatologist, the food elements have usually been thoroughly ruled out and there remain only the other factors. This possibly explains the difference in the point of view, although in my personal experience I see many older patients who have been studied without good results by dermatologists because the element of food allergy has been neglected.

Brain makes the interesting statement that the emotional relationship between mother and child may clearly account for exacerbations of eczema and states that some authorities believe that breast feeding should be discontinued on this account. Focal sepsis may be important, particularly in chronic eczema of the hands and feet. He states that much can be done to toughen the skin by exposure to air and sky shine. The naked skin is stimulated to exercise its powers of adaptation, and there is much evidence that insulation of the skin by overclothing perpetuates the eczematous state. On the other hand, an actinic dermatitis is just as likely to aggravate the condition considerably and, when once acquired, light sensitization may be most difficult to cure.

The Latin-American aspect of infantile eczema has been considered by Salas-Garcia.<sup>74</sup> The literature is reviewed at length and the views of earlier authors, chiefly concerned with etiology, are given. There is no original material and no case reports. There is a section devoted to treatment, chiefly dietetic, with mention of many patent preparations, but this also contains nothing original. It is difficult to abstract a review of this nature.

A very interesting study of infantile eczema with particular reference to inheritance and prognosis has been published by Edgren.<sup>26</sup> The material consists of 395 patients (240 boys and 155 girls) who were studied in Uppsala and Stockholm because of eczema during the first two years of life. The original observations were made between 1903 and 1924. The control material consisted of 465 patients (284 boys and 181 girls). None of these had eczema or any very serious illness.

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Edgren observed that bottle feeding, as compared with breast feeding, did not appear to predispose to eczema. This is directly contrary to the work of Grulee and Sanford.<sup>37</sup> These authors studied the incidence of eczema in 20,061 infants. The results of their investigations showed that the incidence of eczema was lowest in the breast-fed infants. There was twice as much eczema in partially breast-fed infants as those completely breast-fed and seven times as much eczema in bottle-fed as in breast-fed infants.

There was no evidence in Edgren's series that low birth weight predisposed to eczema; the contrary appeared to be true. While girls appeared to develop eczema somewhat later than boys, eczema was more common in boys than in girls. The average duration of the eczema in both sexes was about one and one-half years.

Infants with mild forms of eczema are less likely to have ill health and develop other allergic manifestations than infants with severe eczema. Children whose eczema begins early are more likely to have ill health and develop subsequent allergic manifestations than children whose eczema starts later. The chances of developing chronic atopic dermatitis are greater in those infants in whom the eczema starts early than those in whom it starts late, and are also greater the more widespread the eczema. Edgren found that the frequency of allergy in the family history of children with allergic disease is greater than in the control group. It was also true that the less allergy in the parents, the less apt was the eczematous child to have ill-health and develop other allergic manifestations. Twenty-one per cent of the eczematous children continued to have some form of ill-health and 42 per cent were classified as having unstable health.

Almost 50 per cent of the eczematous children developed some other allergic disease. These, in comparison with allergic manifestations developed by the controls, are as follows:

	<i>Eczematous Children</i> (per cent)	<i>Control Children</i> (per cent)
Urticaria .....	27	6
Asthma .....	23	2
Hay Fever .....	10	2
Strophulus .....	5	2
Angioneurotic edema .....	2	1

Only 10 per cent of the control patients developed allergic disease. The danger to life of infants with eczema appeared to be no greater than when there was no eczema. No cases of so-called "eczema death" occurred in this series.

### ERYTHRODERMIA DESQUAMATIVA

Glaser and Markson<sup>38</sup> have briefly reviewed the literature concerning erythrodermia desquamativa (Leiner's disease). Apparently it is rarely seen in this country in the typical form originally described by Leiner and, when it occurs, is differentiated with difficulty from atopic erythroderma and seborrhoeic dermatitis, exhibiting as it does many features of both diseases. From the data given, the case described is not typical of erythrodermia desquamativa. This condition was suspected because the patient, after suffering from atopic dermatitis which failed to respond to the usual methods of treatment, developed many of the symptoms of Leiner's disease with a scaling dermatitis, intermittent edema, toxemia, diarrhea and finally death. The illness began at the age of three months; a marked change for the worse occurred at the age of seven months, at which time erythrodermia desquamativa was diagnosed; and the child died at the age of ten months. The late date of the onset of the condition and the fact that it followed a typical atopic dermatitis leads the reviewer to believe that it probably was a case of atopic dermatitis of progressive severity which terminated fatally despite all therapeutic efforts. It seems unnecessary to assume that hypoproteinemia is diagnostic of Leiner's disease, since this occurs not infrequently in atopic dermatitis where drastic dietary therapy is attempted.

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A case of the celiac syndrome which developed in an infant who had previously been reported<sup>88</sup> as suffering from Leiner's disease (erythrodermia desquamativa) is noted by Thelander.<sup>89</sup> The celiac syndrome started sometime after the age of eight months, after the patient had apparently completely recovered from Leiner's disease. The child appears to have made a gradual recovery which was almost complete when she was last reported upon at the age of eight years.

Simon<sup>80</sup> has reviewed his interesting work on the relationship between human dander and atopic dermatitis. He found that patch tests with human dander were positive in twenty-six of thirty-one children with atopic eczema. It is difficult to understand Simon's statement that conclusive evidence that foods are important allergic excitants of atopic dermatitis is lacking, in view of the everyday experience of pediatricians with atopic dermatitis unquestionably caused by foods especially milk and usually even more strikingly and unmistakably caused by egg. In my experience with infants up to three years of age suffering from atopic dermatitis, in a series of nineteen cases, positive patch tests with human dander were elicited in seven instances. However, in no instance could a causal relationship be established between human dander and the child's dermatitis. In this connection, Stroud's<sup>83</sup> remark, that the method which Simon advocates for keeping human dander away from an affected child may keep other probable external allergens away and thus benefit the patient indirectly, is very pertinent.

DeForest and Kerr<sup>18</sup> have described an interesting reversal of the usual course of events, in that an infant with infected eczema caused an epidemic of streptococcal infection in a group of nurses working on a pediatric floor rather than the infant's contracting the infection from a nurse. The patient described was a boy, two years of age, admitted with a generalized, fiery red eczema with a left purulent otitis media. Group A, type 14, hemolytic streptococcus was recovered from the skin. Later, the same organism was recovered from nose and throat cultures. During a three-month period, seventy-four nurses took care of this child, and half of them developed streptococcal infections about evenly divided between sore throats and scarlet fever. The parents and relatives who had taken care of the child previous to admission had also developed various infections, presumably of streptococcal origin. This case illustrates the high degree of communicability which hemolytic streptococcal infection in infancy may acquire.

Sulzberger and Baer,<sup>85</sup> commenting upon the above report, state that in their not inconsiderable experience with severe, continually scratched and traumatized atopic dermatitis, they have not seen a single instance of severe invasive infection with staphylococci or streptococci. Four cases of erysipelas complicating atopic dermatitis in infancy were reported by Glaser and Edwards,<sup>35</sup> but the comment of Sulzberger and Baer is essentially correct. While eczematous children not infrequently develop complications caused by cocci, they are nearly always infections of the respiratory or gastrointestinal tract, and the portal of entry does not appear to be the skin. The probable explanation is that the same reactive properties of the skin which result in atopic dermatitis also enable the skin to react effectively against the common skin organisms.

As an illustration of how much in the way of infection a child with allergy may occasionally tolerate, Fischer and McClure<sup>29</sup> report the case of a five-month-old male Negro infant in whom nutrition was a problem because of severe food allergy, manifested in part by eczema, which made intravenous injections difficult or impossible. The child was originally admitted because of eczema, bronchitis, and septic type of temperature elevation. He was hospitalized for 127 days, and during this time he also had clinical evidence of persistent upper respiratory infection, bronchitis, thrush, three episodes of diarrhea, furunculosis of the scalp and forehead, cervical lymphadenopathy, and multiple subcutaneous abscesses. A septic type of temperature curve persisted. The positive laboratory findings were leukocytosis, positive

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cultures for staphylococcus aureus hemolyticus of the scalp furuncles and the subcutaneous abscesses, a predominance of staphylococcus aureus in the throat culture, and one positive blood culture for staphylococcus anhemolyticus. The child responded well to penicillin, which was probably also responsible for other negative blood cultures. Where parenteral amino acids were given, subcutaneous abscesses developed. The authors believe that this was due to secondary infection from the blood stream.

### DIETARY TREATMENT OF ATOPIC DERMATITIS

The use of strained meats, first described by Rowe,<sup>73</sup> and used by Glaser,<sup>32</sup> as a protein basis for milk substitutes in the treatment of milk allergy, has been discussed in the first of these reviews.<sup>33</sup> Since the preparation described was made by a commercial house and was not generally available, Stuart<sup>84</sup> evolved a method by means of which these meats may be prepared in any hospital diet kitchen or even at home. This is done by using one of the small commercial electrically powered homogenizers now on the market. Detailed directions are given.

In the past few months, however, there has appeared another commercial preparation of various finely liquified canned meats. The meat particles in these preparations are even more finely subdivided than those described above and are made by a different process, the nature of which the manufacturers do not care to divulge†. Because of their availability and very fine texture, these preparations should be highly satisfactory as the protein basis for artificial milk substitutes in the treatment of the milk allergy, and I have used them successfully for that purpose.

Fundamental studies in the blood chemistry of eczematous infants with special reference to lipoid metabolism have been continued by Hansen.<sup>39</sup> He states that fatty acids containing two or more double bonds are not synthesized by the body, and certain ones, linoleic acid (C 18 with two double bonds), and arachidonic acid (C 20 with four double bonds), are known in nutrition as the essential fatty acids. In about four-fifths of eczematous infants under two years of age and a little over one-half of adult patients with eczema, the serum iodine numbers were found to be below the normal range.

Hansen, Weise, and Miller<sup>38</sup> were able to raise the iodine number of fatty acids in the serum of dogs by the feeding of lard. This same procedure has been effectively applied to infants with eczema. The lard is spread on crackers or mixed with other foods and appears to be taken well by the patient. It is given in teaspoon or tablespoon quantities once or several times a day as tolerated. A therapeutic trial should comprise a period of about two months or so using 1 to 2 ounces a day.

Obviously, basic work of this nature in eczema is much to be encouraged. However, the difficulties of obtaining satisfactory controls in a disease which is usually self-limited and which at the same time may require other measures than dietary for its amelioration are self evident.

The sedimentation rate, using the Landau-Adams micro method, in fifty-four infants and children suffering from various types of eczema has been studied by Strickler and Ginsberg.<sup>81</sup> The normal rate as established by controls on fifteen children with tinea capitis was between 4 and 9 with an average of 6 with no variation for the male or female group. In the children with eczema, the limits were between 4 and 19 with an average between 8 and 9. The cases were divided into a low group with a rate below 6 and a high group with a rate over 6. The significance of this could not be determined. The sedimentation rate was of no diagnostic or etiologic significance; however, it did reflect to a marked degree the status of the skin provided the child was otherwise normal. An increase in sedimentation rate may be regarded as significant of probable impending complications or an intensification of the inflammatory process. A lowered rate is a fairly good

† Personal communication from Swift and Co., Nutrition Division.

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index of the recovery of the skin, particularly if such a lowered rate persists over a period of time.

An article by Ratner<sup>60</sup> on the subject of infantile eczema, written in popular style for the layman, presents the subject in an interesting and instructive manner. It is recommended reading for the parents of a child with this disease.

### KAPOSI'S VARICELLIFORM ERUPTION

This disease, which was discussed in considerable detail in the second of these reviews,<sup>34</sup> continues to excite interest. Blattner, Heys, and Harrison<sup>3</sup> describe a case of Kaposi's varicelliform eruption in a fifteen-month-old infant with atopic dermatitis. The patient made a good recovery, and herpes virus was isolated from the lesion. Jaquette, Convey and Pillsbury<sup>45</sup> have reported another case with recovery in a six-month-old Negro infant with eczema. The studies suggested that herpes virus, possibly in association with staphylococci and streptococci, was involved in an etiologic relationship in this case.

### CONTACT DERMATITIS

Dobes<sup>22</sup> has described five cases of diaper rash in infants ranging in age from two to sixteen months. The rash appeared as an acute erythema accompanied by a mild edema. Pruritus was present in all cases and vesiculation in one case. Careful studies showed that the rash was due to a preparation called Perm-Aseptic-Ramplex. The purpose of this preparation is to make textiles actively antiseptic, to protect persons as well as to prevent the destruction of textiles by micro-organisms. It is widely used among diaper services in dilutions of 1:10,000 to 1:30,000. Each case cleared in from three to seven days. The patients had worn the treated diapers for at least two months before sensitization occurred.

Pedrer<sup>61</sup> reports the case of a baby five months old who immediately developed a severe dermatitis with edema following the application of highly diluted alibour water to the face and scalp. A patch test on the arm was positive for this preparation which contains sulphur, copper, and zinc. There was no family or personal history of allergy. He also reported the case of a girl twelve years old who was given a drop of argyrol into each eye because of conjunctivitis. There was immediate itching and lacrimation with swelling extending over the lower lids to the cheek. There was no accompanying fever and the patient recovered in three days. The child had previously had some urticaria but there was no family history of allergy.

### URTICARIA

Bivings<sup>2</sup> has discussed in detail a condition which is much commoner in pediatric practice than is generally realized. This is what he terms "acute infectious urticaria." The scant literature on this subject is reviewed and the author reports twenty-two consecutive cases of acute urticaria in children associated with acute infection. The history was negative for allergy in eighteen cases, positive in three, and unknown in one.

The syndrome is characterized by urticaria, usually with angioneurotic edema, fever, and a demonstrable focus of infection. In this series, the throat was most commonly the focus, with otitis media and pyelitis accounting for the remainder. The urticaria could not be explained on the basis of drug sensitivity or the ordinary allergic types of sensitivity except in one case. Four typical cases, ranging in age from ten months to seven years, were reported. The limited bacteriological study showed no common organisms. The youngest patient was described as having a fever of 37.8° C. (100° F.) rectally. While it must be admitted that the standard for a normal rectal temperature in infants and children has never been officially established, it is the reviewer's practice to regard no rectal temperature as evidence of fever unless it is over 37.8° C. (100° F.). Even higher temperatures, at least

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up to 38.7° C. (101° F.) may occur in the absence if the temperature happens to be taken after exercise.<sup>7,41</sup> It must be remembered in this connection that crying is a form of exercise in this age group.

It is well known that urticarial eruptions resembling the papular urticaria of older children occur in the newborn. Indeed, urticaria may be regarded as the first clinical manifestation of allergy to occur in the human being. Ström<sup>82</sup> made an interesting study of this condition by feeding fifty-eight recently delivered mothers three oranges a day during their stay in the hospital. Urticaria appeared in twelve (22 per cent) of the nursing infants of the test group and in only two (3 per cent) of the control group. Urticaria could not be produced by feeding the mothers 100 mg. each of ascorbic acid daily, so presumably the rash was not due to vitamin C. There were two cases of very extensive urticaria in the infants of the orange-fed mothers. The rash disappeared soon after withdrawing the oranges from the diet. In one of these, the urticaria recurred when the mother was fed orange again. In the course of the study, a case similar to this latter was observed due to chocolate ingested by the mother. The author further states that drugs administered to the mother must also be considered as a possible cause of urticaria in the nursing infant.

Eder,<sup>25</sup> in discussing the prophylaxis and treatment of allergic disease in early infancy, advises elimination from the diet of the nursing mother of what he has found to be the five most common offenders: cream, oatmeal, egg, chocolate and nuts (including peanut butter). The only one of these in reviewer's experience which has ever caused trouble has been egg. Chocolate does cause trouble, as mentioned in the preceding paragraph, and the first clinical report on this subject of which I am aware was that of Talbot<sup>87</sup> who reported that eczema could be cured or produced in the case of one individual baby by withdrawing or including chocolate in the mother's diet. The peanut is regarded as a nut by most laymen and many physicians. It is, however, not a nut but a legume (pea and bean family) and since legumes tend to react as a group, if one causes trouble it is best to avoid all until the guilt or innocence of each is proven.

The use of benzedrine sulphate for the treatment of urticaria in children has been advocated by Roberts.<sup>70</sup> In the cases of ten children with urticaria varying in age from two and one-half to six years, benzedrine sulphate was used in starting doses of 2.5 milligrams every three to four hours. All children were relieved except one child, three and one-half years of age, who had developed urticaria seven days after receiving tetanus antitoxin. Two children, aged four and nine years, respectively, required 5 milligram doses every four hours for relief. One child six years of age with chronic urticaria was relieved twice by benzedrine sulphate and then disappeared from observation. Disagreeable side reactions from the use of this drug, particularly wakefulness, excitement, and loss of appetite, were not mentioned. The author recommends that fluids and laxatives also be employed properly in this condition. This report is of considerable interest, particularly with regard to the reaction of children to benzedrine. However, the reviewer believes, because of personal experience with these preparations, that benadryl and pyribenzamine will be the drugs of choice in the treatment of urticaria and angioneurotic edema in this age group as well as in older children and adults.

## POLLINOSIS

A case of hay fever occurring in New Jersey in a four-month-old boy was reported by London.<sup>54</sup> The symptoms were characteristic for the disease. The scratch tests showed positive reactions to short and giant ragweed and cocklebur. Treatment by the injection or ragweed extract was started and symptoms were greatly alleviated within a few days. This case was first treated in August of 1942.



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There was no recurrence of the hay fever in subsequent seasons. This is interesting since he received no treatment after the first season. The author states that this case suggests the possibility that early institution of hay fever treatment during the first season of its occurrence may result in a rapid cure. The age at which hay fever may start doubtless depends upon the susceptibility of the individual and the amount of pollen present in any given locality. Kahn<sup>46</sup> states that in certain parts of Texas newborn infants may develop symptoms of pollinosis shortly after birth. The youngest patient I have seen with hay fever was an infant six months of age. The symptoms were mild the first year, and treatment was not instituted until they again recurred when the child was eighteen months of age. She has required continuous treatment since then, and the child is now sixteen years of age.

### OTITIS

Hiller<sup>42</sup> has reviewed the subject of allergic otitis media with particular reference to the work of Hansel, Proetz and other Americans. The author reports the case of a fourteen-year-old girl with a history of allergy (perennial allergic rhinitis and urticaria) who gave a marked reaction to a staphylococcus vaccine. She had four attacks of otitis media, one of which was followed by mastoiditis. Angioneurotic edema of the face and allergic rhinitis had always preceded and accompanied the attacks of otitis. The condition was kept under control by vaccine, and there was no further recurrence of the otitis.

### PURPURA OF ALLERGIC ORIGIN

An interesting case of Henoch-Schönlein purpura and acute nephritis due to food allergy is reported by Brown.<sup>8</sup> A nine-year-old boy had been hospitalized three months before the present reported admission because of colicky abdominal pain, vomiting, bloody stools, a stiff left hip joint, and a purpuric rash on the trunk. Because of rigidity and tenderness in the right iliac fossa, it was felt necessary to do an appendectomy. This revealed a kinked but otherwise normal appendix, which was removed without relief of the patient's symptoms. Over a period of one month after operation the symptoms gradually subsided and the patient was discharged. He was again readmitted to the hospital three months later because of blood in his stools of two weeks' duration. His urine was normal at that time. After a week's observation, he was discharged with a diagnosis of allergic purpura. The week following, he had two attacks similar to those for which he had been hospitalized three months previously, also accompanied by urticaria and hematuria.

It was observed that both of these attacks occurred on Sunday and each attack occurred two hours after the evening meal containing various foods including tomatoes. By elimination diets, it was found that the symptoms could be reproduced by feeding tomatoes, and on two occasions the boy gave positive scratch tests to the pulp but not to the skin of tomatoes. Tomatoes were omitted from his diet, but three months after the last attack, the urine contained red and white blood cells and granular casts, though there had been no symptoms during that time.

The literature of this subject is reviewed, and the author states that he saw a patient who came to autopsy with chronic nephritis eleven years after an atypical attack of allergic purpura associated with hematuria. When bacterial allergy is the apparent cause, the probability of recurrent attacks and repeated damage is considerable. Where food allergy is responsible and the offending food is avoided, the prognosis may be less serious.

Njå<sup>50</sup> has reported a case in a year-old child of what is probably another variety of allergic purpura, occurring in a younger age group and first described by

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Seidlmayer<sup>77</sup> in 1939 under the name of "Die frühinfantile, postinfektiöse Kokarden-Purpura." This disease occurs in infancy and childhood up to the age of three years and is commonly associated with upper respiratory infection. Characteristic purpuric eruptions appear, which may be as large as the infant's hand in some cases. These usually occur in the center of urticarial or edematous areas and are localized chiefly to the extensor surfaces of the extremities, the buttocks and face. Hematuria is uncommon but occurred in Njá's case. In this case also, skin tests with bacteria were negative except to pneumococci, which gave large hemorrhagic reactions. This suggests allergy to infection. The prothrombin time in this case was greatly prolonged (in excess of five minutes) and this became normal when the hemorrhage ceased. The disease is closely related to Hennoch-Schönlein's purpura and differs from this mainly through its occurrence under six years of age and the absence of joint and abdominal symptoms. It might be regarded as another variety of this disease in a younger age group.

### PERIARTERITIS NODOSA

Two cases of periarteritis nodosa occurring during the first month of life and discovered at autopsy are reported by Wilmer.<sup>94</sup> This brings to four the number of reported cases of this disease occurring during the first year of life. Both of Wilmer's cases occurred in colored children. In both, there was leukocytosis but no eosinophilia, and typical foci of periarteritis nodosa were found in various organs. The first patient was a girl who developed symptoms at the age of twenty-five days and died twelve days later, at which time the probable clinical diagnosis was septicemia or renal thrombosis. The only family history of allergy was in the case of the mother who had hives from tomatoes. At autopsy, there was a large inflammatory-necrotic mass involving the right adrenal, containing large numbers of unidentified cocci. The second case was a boy who died at the age of ten days after an illness of two days. Pus could be expressed from his umbilicus and it was believed that he had a septicemia. The family history for allergy was not obtainable.

### DRUG ALLERGY

The incidence of reactions to sulfonamide drugs in an estimated 5,000 infants and children is reported by Fink and Smith.<sup>28</sup> Most of the patients received sulfadiazene, some sulfathiazole and some sulfamerazine. Sixty patients (1.4 per cent) developed febrile reactions, twenty-five with accompanying rashes. There were only eight additional important complications: two cases of malignant neutropenia, two cases of hemolytic anemia, and four cases of anuria. All recovered except two cases of anuria, both of which had received sulfathiazole. Over half (59 per cent) who proved sensitive to one course of sulfanilamide developed immediate reactions to tests with repeat doses. Test doses of 0.25 gm. (grains 3.8) were usually sufficient to produce a reaction. Immediate reactions were observed only in those patients who had shown previous drug reactions. Seven children were given test doses of a sulfonamide different from that to which they were proved sensitive. Only two developed reactions and both of these received a third sulfonamide without trouble. Skin-testing of suspected sulfonamide sensitive patients with human sulfonamide-containing serum, after the manner of Leftwich,<sup>51</sup> was not found useful by the authors. Renal complications were rare, and the authors feel that it is unnecessary to supplement sulfonamide therapy with alkali. They conclude that untoward reactions to sulfonamides are infrequent in infants and children and rarely cause serious effects.

Pedreira<sup>61</sup> has reported six interesting cases of drug allergy in children. Two of these were due to acetylsalicylic acid. One occurred in a boy twelve years of age who had never before taken any preparation containing this drug. Follow-

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ing the taking of a popular headache remedy, there was a sudden edema of the eyelids and loss of voice due to edema of the larynx. This was followed by dyspnea, dysphasia, and intense headache. Complete relief was very rapidly obtained from the injection of epinephrine. The patient was known to be allergic to chocolate. He had had asthma as an infant and also had a mild perennial allergic rhinitis. There was no family history of allergy. Whenever he ingested acetylsalicylic acid, he would develop atopic dermatitis and occasionally bronchitis and coryza with edema of the lids.

Three cases of allergy to sulfonamides are described. One occurred in a girl twenty-two months of age who was given sulfanilamide because of a sore throat. On the second day after starting the medication, each dose was followed by vomiting, pallor, cyanosis, and alarming peripheral circulatory failure. Recovery was complete within two days after stopping the drug. The child had never before taken any sulfonamide drugs. The second case was a boy fifteen months of age who was given sulfathiazole because of tonsillitis. On the third day there was a generalized maculopapular eruption and swelling of the lids. This was unaccompanied by fever. The rash disappeared on the fourth day. There was no history of previous sulfonamide treatment and no family or personal history of allergy. The third patient was a girl seven years of age who received sulfonamides on several previous occasions for tonsillitis. The family and past personal history as far as allergy is concerned was not mentioned. About two weeks after the last attack of tonsillitis, oral sulfathiazole was administered because of fever and cervical lymphadenitis. Three days later an eruption appeared which quickly spread over her entire body. This was at first bright red but changed rapidly in appearance and disappeared on the fourth day. The rash was accompanied by high fever the first two days.

Two other cases were due to sensitivity to mercury. One was a girl eight years of age who would develop dyspnea caused by merthiolate in nasal drops. She had previously had a contact dermatitis caused by a green dye in a dress. This dye was not identified but patch tests to the green cloth were positive. Her history revealed mercurial ointment used for suspected syphilis had previously provoked such an intense dermatitis that it had to be discontinued. There was no family history of allergy.

Another patient, a girl seven years of age, had what was probably cyclic vomiting. Usually, intramuscular injection of luminal had given good sedative results, but on her last attack this reacted in the opposite manner, causing great excitement. Cutaneous tests were positive for several foods and the child seemed to improve after these were excluded from her diet.

A boy eight years old had a fixed eruption, more pigmented than inflammatory, on the anterior portion of both legs. This was shown to be due to phenolphthalein which had been used as a coloring matter in tooth paste.

Pedrerá believes that drug allergy is the most appropriate term to describe the majority of abnormal reactions to medicinal drugs.

In another publication, Pedrerá<sup>63</sup> stresses the dangers of the therapeutic and prophylactic injections of horse serum in children. He advises the use of serum derived from other animals when possible but does not consider this very practical. It is unfortunate in this connection that the manufacture of bovine tetanus antitoxin<sup>81</sup> in this country has been discontinued. The use of toxoid for prophylaxis is stressed. This article is largely derivative and there are no original case reports.

## PSYCHOSOMATIC ASPECTS OF ALLERGY

Bowen<sup>4</sup> expresses the opinion that while allergic children as a group present some interesting extremes as regards mentality, if taken as a class they show no more variation in mental ability than the average. It should be emphasized with

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these children that they are expected to follow the same principles of social responsibility for the rights and privileges of others as the nonallergic group.

The hyperkinetic child is the patient described by Schneider<sup>76</sup> who is commonly recognized as the "nervous child," or the "fidgety child," or the child who "never sits still." Among the physical abnormalities contributing to hyperkinetic behavior, the author discusses the role of allergy, and states that possibly too little attention is given by the general physician and pediatrician to the role of allergy in either causing or accentuating emotional disturbances. He quotes Karnosh<sup>47</sup> as stating, "It becomes more and more evident that this reaction (i.e., allergy) involves every level of the nervous system from the highest and most elaborate centers of the cortex to the humblest sympathetic terminal in the capillary loop of the skin." The author also reviews the work of Clarke<sup>13</sup> with reference to allergy as a cause of cyclic vomiting, infantile convulsions, temper tantrums, petit and grand mal, abdominal pain, inattention, unruliness, surliness, disobedience, and incorrigibility.

Schneider describes the case of a hyperkinetic ten-year-old child who started out life with pylorospasm followed by many food allergies and later insomnia. Her activity was so excessive, at times amounting to wildness, that she was placed in nursery school at the age of two and one-half years. By the time she was eight and one-half years of age, her hyperkinetic drive was so disrupting to the family that she was placed in boarding school. Recurrences of attacks of uncontrolled behavior led to hospitalization at the age of nine and one-quarter years. Here she gave numerous positive skin tests, and therapy from the allergic standpoint was followed by marked amelioration of the child's behavior problems within a three-month period.

Dees<sup>17</sup> states that in the complex problem presented by the allergic child, psychiatric factors often play a major role and are more often closely related to the production of illness than any other single nonallergic factor. Several very interesting case histories are reported. One was a twelve-year-old dust sensitive asthmatic boy who did very well for a year on the usual measures employed for the treatment of this condition. The asthma recurred when his father entered a hazardous branch of the military service. It was discovered that the boy had a marked feeling of insecurity without his father and this feeling was unconsciously made even worse by his mother's attitude towards the problem. The asthma promptly stopped when the door of the boy's dust-free bedroom was left open at night so that he felt less isolated.

Another case was a boy seven years of age whose parents were separated. The boy had asthma every time he was taken to stay with his father in town. He was clinically sensitive to pollens and farm animals but remained relatively well while living with his mother on a farm. He had asthmatic attacks whenever his parents quarreled.

These two cases represent one of the commonest forms of maladjustment seen in asthmatic children. This results from a fundamental feeling of insecurity due to over-attachment to one of the parents. This is secondary to the over-protection which the child suffers as a result of the allergy.

The allergic child who uses his affliction to obtain fulfillment of his wishes or to avoid anything disagreeable is well known. Dees describes the case of a nine-year-old asthmatic girl who, although completely asymptomatic, could bring on an attack of asthma at will when confronted with something unpleasant, such as impending skin testing. In this particular case, allergic measures were successful with the exception of occasional attacks of asthma when her desires were thwarted.

Abnormal behavior may occur as a chronic condition in practically all allergic diseases. The most common complaints are over activity, hyperirritability, sleeplessness, unreasonableness, thumb sucking, enuresis, and temper tantrums. Exacer-

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bation of these symptoms may precede an exacerbation of the allergic condition. One of the earliest signs of improvement in the underlying allergic condition may be evidenced by parallel improvement in disposition and behavior.

Dees states that investigations now in progress seem to indicate that a large number of children with asthma and eczema have abnormal electroencephalograms which tend to become normal with control and improvement of the allergy. She reports one ten-year-old child with a slightly abnormal electroencephalogram who suffered from head bumping. This appeared to be very definitely related to his allergy. These observations recall the work of Shulman<sup>78</sup> on the use of dilantin sodium in bronchial asthma. The reviewer gave this a fairly extensive trial in an unselected number of cases (asthmatic children whose electroencephalograms had not been studied because facilities were not then available) without beneficial results.

Dees states that she has been unable to find children with eczema or urticaria on a purely psychogenic basis such as is seen in adults. She notes that there does appear to be an occasional epileptic child who is relieved by allergic management without other drug therapy.

Arena,<sup>1</sup> in discussing the above presentation, expressed the point of view which is probably favored by most pediatric allergists, namely that many of these behavior problems are secondary and not primary. By this is meant that they are secondary to the stress and strain brought on by the allergic attacks. If the child did not have these attacks, the chances of his developing a behavior problem would be greatly diminished. Arena also makes the statement that, during an asthmatic attack, the parents and others at home with the child are very often in a state of fright and disorganization. Besides specific therapy for relief of the asthmatic attack, the child needs to be in a calm, quiet, reassuring atmosphere. This point has also been stressed by Bowen.<sup>1</sup> Continuing the discussion on these presentations, Lowenbach<sup>5</sup> states that one should not too readily seek the assistance of a psychiatrist in children with allergy but that every effort should be made to solve the problem from the allergic standpoint. If this does not appear to be progressing satisfactorily, then the parents may be gradually prepared for co-operation with a psychiatrist.

## DRUGS

Logan<sup>53</sup> has briefly reported on the use of benadryl in the treatment of eighteen children suffering from various allergic diseases. Both the elixir, which contains 10 mg. of benadryl per 4 c.c. (teaspoon), and the capsule, which contains 50 mg., were used. Where a fraction of a capsule was used, the powder was removed and administered in syrup or jelly. In the whole group of eighteen children, only two untoward reactions, drowsiness and vomiting, occurred. The suggested dose of benadryl is 2 mg. per pound of body weight per twenty-four hours, divided into from two to four doses. The frequency of administration should depend upon the duration of the effect, which may last from two to twelve hours. The effect should be noted within thirty or forty minutes as a maximum. Twelve of the patients had seasonal hay fever and were treated only during the season. Three of the patients had asthma. The results of the treatment of the hay fever were recorded as excellent or good in nine cases, fair in one, questionable in one, and no effect in one. The results on associated asthma which occurred in three cases were recorded as good in one case, fair in one, and questionable in another. One two-year-old child with urticaria was completely relieved. Of two children with vasomotor rhinitis, one received excellent relief and the other apparently very good relief.

One patient three years old with nephrosis would have an urticarial reaction following every infusion of plasma. The administration of benadryl before and after this procedure gave great relief to this condition. One case of angioneurotic

edema and urticaria following tetanus-gas gangrene antitoxin received complete relief from benadryl.

The reviewer is of the belief that benadryl and pyribenzamine are of considerable help to the pediatrician. The full extent to which these drugs may be used with reference to the conditions in which they might be indicated has not yet been explored. Both benadryl and pyribenzamine have been used extensively in my practice and, as nearly as I can tell, their effect and side reactions are practically identical. Occasionally, one of these drugs will be of assistance where the other one will not. Also occasionally, one of the drugs will cause disagreeable side reactions and the other will not. It is fortunate to have two such drugs so that one may be tried when the other one will not help or does not agree. In general, these drugs give remarkable relief in urticaria; they are of great assistance in the sneezing and running nose of hay fever; they are of a fair amount of help in perennial allergic rhinitis; their use in bronchial asthma is disappointing. Occasionally, a patient appears to get very definite relief. I have the impression that this occurs especially when the asthma is due to food allergy. They give no relief in intrinsic asthma. These drugs are also of considerable value in relieving the pruritis of atopic dermatitis and also are worth trying in pruritis of any other origin which has not responded to the usual measures of treatment. However, here the effects are variable and inconstant.

In the first of these reviews<sup>33</sup> it was stated that privine for use in nose drops was supplied in two strengths, 0.1 per cent and 0.05 per cent. It was further stated that these two strengths were used because at times the drops appeared to cause sedation. This cannot happen very often because but one report of this condition, that of Waring,<sup>32</sup> has appeared since privine was introduced several years ago. He reports the cases of two girls, ages three months and seven years, respectively, who, following the administration of privine hydrochloride 0.05 and 0.1 per cent respectively in the appropriate doses, developed marked somnolence. Another boy, three years of age, drank an unknown amount, probably 7 or 8 c.c., of privine hydrochloric 0.05 per cent. He soon became quite drowsy and remained so for several hours afterwards.

Boric acid ointment is a preparation which is very commonly used in the treatment of infantile eczema. While it is well known that boric acid solution by mouth may be highly toxic to infants and young children, it is not generally realized that rarely it may also be toxic as an ointment. Watson<sup>33</sup> has briefly reviewed the literature on boric acid poisoning. He states that boric acid is a drug which is almost entirely ineffective and may be dangerous, even when used in ordinary ways. He reports the case of a four and one-half-month-old boy with severe generalized weeping infantile eczema, treated first with boric acid soaks for two days and then with boric acid ointment for two days. The infant developed fever, convulsions, and an intense generalized erythema. The convulsions gradually ceased, but the child became deaf and then comatose and died three weeks after the onset of the convulsions.

Repeated spinal fluid examinations were negative for evidence of infection until a few days before death, when the child developed a terminal pneumonia and pneumococcus meningitis. Tests for boric acid in the spinal fluid and urine were strongly positive during the first week. The diagnosis of boric acid poisoning was suggested by the similarity in behavior of this child to infants accidentally poisoned by boric acid. The intense erythema, giving the child the appearance of a boiled lobster, is an outstanding characteristic.

Boric acid ointment is further discussed by Pfeiffer, Hallman and Gersh.<sup>34</sup> They state that boric acid, whether applied in the form of an ointment or a saturated solution to extensive wounds, is a cumulative poison. The weak antiseptic value of boric acid suggests that, for medicinal use, other more active and less po-

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tentially harmful therapeutic agents should be employed. The best antidotes for boric acid poisoning are the intravenous administration of plasma and large intravenous injections of isotonic solution of chlorides.

### HAPAMINE

Anyone who attended the annual meeting of American Academy of Allergy in December, 1945, would have been convinced that as a therapeutic agent hapamine was without value except perhaps as a nonspecific therapeutic measure whose use was not without danger. Eder<sup>25</sup> has since reported the use of this preparation in seventeen cases of allergic rhinitis in children, fourteen of whom were under the age of five years. Seven cases had asthma and three had atopic dermatitis. It is stated that the results have been almost too good to be believed and all the allergic manifestations in these patients were apparently benefited by the hapamine. Three illustrative case reports are given. In the first case, the hapamine treatment was started in September, 1945, and the child showed improvement from the first dose; in the second case, treatment was started in October, 1945; in the third case, the history does not mention that the child had allergic rhinitis but she did have recurrent upper respiratory infections and asthma. All these children were apparently completely relieved. Treatments were started in December, 1945. Since the article was published in May, 1946, it must have been submitted for publication at least a month earlier. Therefore, even if one grants immediate improvement from the time of starting of the hapamine therapy, the longest interval of relief was five months. It is my experience that one cannot be sure that any single measure has produced complete relief of allergic rhinitis unless the duration of relief is at least one year. In this part of the country (New York State) many children with perennial allergic rhinitis suffer exacerbations during the summer because of pollen. This is especially true in the last part of August and September when the ragweed pollen is especially plentiful. Any therapeutic measures administered at this time will often appear to give relief because from then on the atmospheric pollen gradually diminishes. For this reason, I do not consider any patient to have obtained satisfactory relief from any therapeutic agent administered unless he has been free from symptoms for at least one year or a complete pollen cycle. While pollen conditions are doubtless different in Santa Barbara, California, than in Rochester, New York, the same principle doubtless obtains. A report from Eder after a few years on the condition of these patients would be a useful contribution to our knowledge of hapamine. My personal experiences with this drug have been both disagreeable and unsatisfactory.

### MISCELLANEOUS

A detailed study of 289 cases of allergy in children has been reported by Torroella.<sup>90</sup> The children were classified according to their major allergic disease as follows:

	Cases
Asthma .....	124
Urticaria .....	81
Chronic Atopic Dermatitis (Hebra's prurigo).....	26
Allergic Rhinitis (vasomotor rhinitis).....	21
Atopic Dermatitis .....	17
Infantile Eczema .....	16
Allergic Purpura .....	1
Migraine .....	1
Gastro-intestinal Allergy .....	1
Contact Dermatitis .....	1

Under each subdivision of the above, the author gives the results of skin tests, therapy, and his result. In his practice, allergic children make up 17.1 per cent

of the total number of allergic patients. More patients (42.6 per cent) belong to the second period of childhood than to the first or third period. Asthma is the most frequent manifestation (42.9 per cent) and urticaria the next (28 per cent). The various skin allergies make up 48.2 per cent of the total.

Family histories of allergy may be established in 76.4 per cent of the cases. Hereditary transmission is mostly through the mother. The average age at which symptoms begin is 4.4 years. The proportion of male to female is 1:1.3. More than one allergic manifestation in the same patient was noted in ninety-four cases (32.5 per cent). For the entire group, clinical cure was reported in 32.7 per cent of cases; great improvement in 29.8 per cent; improvement in 33.9 per cent; and no improvement at all in 3.4 per cent of the cases.

While no one believes that the continuous administration of a sulfonamide compound to prevent upper respiratory infection is an ideal procedure, yet in the desperate attempt of the pediatric allergist to relieve those children who develop asthmatic attacks regularly following such infections, it has been felt that the risk of this procedure is well justified. The value of so doing, however, is still open to question. In this connection, the report of Siegel<sup>79</sup> on the incidence and severity of acute infections of the upper respiratory tract in 128 physically normal children, half of whom were treated by the continuous oral administration of sulfadiazine and half of whom were untreated, is of considerable interest. The drug was used between August, 1942, and April, 1944, for periods of four to fifteen consecutive weeks in doses ranging from 0.5 to 2 grams daily. The average level of free sulfadiazine in the blood was 3.5 mg. per cent with a maintenance dose of 1 gram per day and 7.2 mg. per cent with 2 grams per day. In no case was it necessary to discontinue the use of the drug because of serious toxic reactions.

The incidence of acute infections of the respiratory tract was almost the same for treated and for controlled children. However, the treated persons as a group recovered somewhat more promptly than the controls and experienced fewer complicated illnesses and fluctuations in severity. Since the illnesses observed were unexpectedly few and were milder than anticipated, the antibiotic effects of sulfadiazine were not readily demonstrable.

Kendrick, Thompson and Eldering<sup>48</sup> have contributed to the study of the puzzling lack of immunity to pertussis in the newborn, without, however, solving this problem. A group of pregnant women was treated with pertussis vaccine (it is not stated that Phase 1 was employed) and another group used as a control. The opsonic reactions in the treated group were twice as strong as in the untreated group and in the babies of the treated mothers were about 2.9 times that of the control group. In the treated group the babies had two-thirds of the opsonic activity of their mothers. Perhaps the lack of immunity to whooping cough in the newborn may be explained upon a quantitative basis; that is, the level of immunity in mothers is generally too low for effective protection of their offspring. Conclusions on this basis cannot be made, since it is not known what correlation there is between opsonins and protection. The results indicate that placental transfer of circulating pertussis antibodies does occur and that the higher the level in the mother the more nearly does the titer of her baby approach her own. The study indicates that under certain conditions it may be practical to treat the pregnant mother with pertussis vaccine in order to raise the level of immunity in her baby.

It seemed generally agreed, according to Rollof,<sup>72</sup> that erythema nodosum is an allergic skin reaction induced by different infections in individuals who have a predisposition for this disease. In tuberculosis, erythema nodosum usually appears at that stage of the process where the tuberculin reaction is changing from negative to positive. The author studied thirty-three children with primary pul-



monary tuberculosis. Erythema nodosum was provoked in twelve cases by the administration of sulfathiazole. It occurred in all cases where the patients were still in the initial fever stage of the tuberculous process. Roloff states that practically all cases of erythema nodosum occurring in children with acute infections, treated with sulfathiazole occur in association with recent tuberculous infections.

It is suggested by Epstein and Custer<sup>27</sup> that two peculiarities of acute lymphatic leukemia in childhood point to sensitization phenomena. These are the frequent association of its onset with infection, and the recurrence of remissions with apparent complete clinical recovery. They report a case of aleukemic lymphatic leukemia in a twenty-month-old girl who presented clinical evidence of sulfonamide sensitivity. Their studies raised the suspicion that hypersensitivity may play a role in the mechanism of leukemia, at least in that form in which it presents itself in early childhood.

Hatoff<sup>40</sup> treated 129 susceptible infants and children of an average age of four years by injection of an extract of the whole fleas of dog, cat and man. Each of these children had suffered unabatedly from flea bites for a period of from one week to one year. Of the treated cases, 78 per cent were benefited, 5 per cent received equivocal relief, and 17 per cent failed to respond. The work of Eder<sup>24</sup> in connection with flea bites is also interesting. He reports marked success in the prevention and treatment of flea bites by the oral administration of thiamin chloride. The thiamin is given three times a day for three days. In the case of infants, the dose is 10 mg.; runabout children, 20 mg.; older children, 30 mg.; and adults, 40 mg. This is followed by a smaller daily dose for several weeks.

Attention is called to the publication of a new journal, *The Quarterly Review of Pediatrics*.† This contains abstracts and book reviews of all subdivisions of pediatric literature. These are classified alphabetically under thirty-four headings, the first of which is "Allergy." In a work of this scope, the number of abstracts of articles in the field of allergy is naturally limited, but they are exceedingly well done, timely, and will be of great help to the pediatrician.

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†Published by the Washington Institute of Medicine, 1720 M Street, N. W., Washington 6, D. C. The price is \$9.00 a year.

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(Continued on Page 92)

# News Items

## SPECIAL SESSION ON ALLERGY OF THE AMERICAN MEDICAL ASSOCIATION

On Thursday, July 4, 1946, a committee representing the American Academy of Allergy and the American College of Allergists, appeared before the Reference Committee on Sections and Section Work of the American Medical Association.

A report of the Reference Committee on Sections and Section Work (J.A.M.A., July 20, page 1000) concludes, "After consideration of the information as presented by the reports of the Academy and the American College of Allergists, the Reference Committee recommends that the question be referred to the Council on Scientific Assembly for study and recommendation."

The latter Council has arranged for a special session on Allergy to be held at the Centennial Meeting of the American Medical Association at Atlantic City on Friday, June 13, from 2 to 5 p.m. This special session will serve as a guide when establishing a Section on Immunology and Allergy. Dr. Harry Huber has been appointed chairman of the special session and Dr. Richard Kern, secretary.

Although this special session is to be held on the last day of the American Medical Association meeting, five days following the closing of the session of the American College of Allergists at the Hotel Senator, June 6, 7, and 8, every member of the College is urged to attend this meeting and help make the program a success. The program will undoubtedly be arranged to arouse the interest of the general practitioner in allergy and in no way will it conflict with the scientific session to be held by the College. If the Council on Scientific Assembly of the American Medical Association establishes a Section on Allergy or a Section on Immunology and Allergy, it means the recognition of allergy as a specialty.

This session will be observed very closely, and its future success will eventually depend upon the co-operation of the two national allergy societies by having equal representation.

\* \* \*

## SOUTHWEST ALLERGY FORUM

March 31 and April 1, 1947

WASHINGTON-YOUREE HOTEL

Shreveport, Louisiana

SUNDAY, MARCH 30, 1947

8:00 P.M.—Cocktail Party

At the home of Dr. H. Whitney Boggs, 140 Albany Street

MONDAY, MARCH 31, 1947

Morning Session—9:00 a.m.

Some Faults in the Allergist's Routine

DR. GEORGE L. WALDBOTT, Detroit, Michigan

Discussion opened by DR. H. WHITNEY BOGGS, Shreveport, La.

Pathology of Allergy—A Bridge to Understanding Clinical Allergy

DR. BERNHARD STEINBERG, Toledo, Ohio

Discussion opened by DR. L. O. DUTTON, El Paso, Texas

Evaluation of Aerosol in the Treatment of Asthmatic Bronchitis

DR. BOEN SWINNEY, San Antonio, Texas

Discussion opened by DR. NARCISSE THILBERGE, New Orleans, La.

Lunchcon—12:30 P.M.

Washington-Youree Hotel, Zephyr Room

## NEWS ITEM

### *Afternoon Session—1:30 P.M.*

Round Table—Nutritional Problems in Allergy\*

Leader: DR. ROBERT STONE, Birmingham, Ala.

Co-ordinator: DR. HERBERT RINKEL, Kansas City, Mo.

Greetings

CLYDE E. FANT, Mayor, City of Shreveport

DR. C. WEBB representing the Shreveport Medical Society

Round Table—Dermatological Allergy\*

Chairman: DR. DUDLEY YOUMAN, Shreveport, La.

I. Where is Allergy Indicated in Dermatology? DR. DUDLEY YOUMAN, Shreveport, La.

II. Non-contact Causes of Allergic Dermatitis. DR. MAURICE C. BARNES, Waco, Texas

III. Contact Dermatitis

(A) Plant Oils. DR. GEO. T. SEIBOLD, Houston, Texas

(B) Cosmetics, Dyes and Drugs. DR. ELLIS P. COPE, Little Rock, Arkansas

(C) Preparation of Poison Ivy Extracts. DR. LAWRENCE HALPIN, Cedar Rapids, Iowa

Rationalization in Allergy

DR. J. HARVEY BLACK, Dallas, Texas

### *Evening Cocktail Party and Banquet*

#### *Cocktail Party—6:00 P.M.*

Washington-Youree Hotel—Mezzanine Floor

#### *Banquet—7:00 P.M.*

Vitamin Deficiencies—Emphasis on Recent Developments

Guest Speaker: DR. ROBERT STONE, Nutrition Clinic, Hillman Hospital, Birmingham, Alabama

The Symphony of the Seasons

A Color Rhapsody of Winter, Spring, Summer, Autumn

DR. HERBERT J. RINKEL, Kansas City, Mo.

## TUESDAY, APRIL 1, 1947

### *Morning Session—9:00 A. M.*

Aerobiology: Evaluation of Air-borne Allergens

MR. O. C. DURHAM, Chicago, Illinois

Discussion: MR. H. L. GRAHAM, Dallas, Texas

Follow-up Reports on Previous Papers

DR. F. R. RUGELEY, Wharton, Texas

DR. PAUL T. PETTIT, Beaumont, Texas

Round Table—Treatment of Hay Fever

Chairman: DR. BERNARD G. EFRON, New Orleans, La.

Leaders: DR. MARY HEWITT LOVELESS, New York City; DR. FRENCH K. HANSEL, St. Louis, Mo.; DR. OSCAR SWINEFORD, Charlottesville, Va.

Co-ordinator: DR. FRANCIS M. RACKEMANN, Boston, Mass.

### *Luncheon—12:30 P.M.*

Washington-Youree Hotel, Zephyr Room

### *Afternoon Session—1:30 P.M.*

Open Forum—Evaluation of New Drugs in Allergy\*

Leader: DR. JOE S. SHAVIN, Shreveport, La.

Allergy in Relation to Cardiovascular Problems

DR. TINSLEY R. HARRISON, Dallas, Texas

Discussion opened by DR. SIM HUSLEY, Fort Worth, Texas

The Classification of Asthma

DR. FRANCIS M. RACKEMANN, Boston, Mass.

Discussion opened by DR. ALAN CAZORT, Little Rock, Arkansas

Allergic Problems in Children

DR. JEROME GLASER, Rochester, New York

Discussion opened by DR. RALPH BOWEN, Houston, Texas

Business Session—Southwest Allergy Forum

\*What is your opinion? What are YOUR PROBLEMS? COME PREPARED TO DISCUSS.

NEW YORK ACADEMY OF SCIENCE

Tentative Program—Friday, April 25

1. Experimental Anaphylaxis in Lower Animals  
Beatrice Seegal
2. Allergic Disease in Lower Animals  
(Classification of Allergic Diseases)  
Lester A. Reddin
3. Serum Sickness  
Samuel Karelitz  
Discussion: Bela Schick
4. Contact Allergy (Epidermal)  
Max Grolnick
5. (a) Allergy of Infection (Relation to Immunity)  
Beatrice Seegal  
(b) Allergy of Infection (Fungi and Fungous Products)  
Marion B. Sulzberger
6. Atopic Allergy (Reaginic sensitivity)  
Matthew Walzer  
Discussion: Stuart Mudd, Sanford B. Hooker
7. Familial Nonreaginic Allergy  
Milo G. Meyer
8. Familial Nonreaginic Allergy as a Predisposing Cause of Common Cold  
Arthur P. Locke
9. The Anti-allergic Action of Sympathectomy  
Arthur F. Coca

\* \* \*

Dr. Stephan Epstein is now Clinical Associate Professor of Dermatology and Syphilology at the University of Minnesota.

\* \* \*

William H. Horwitz, M.D., announces his release from military service and the opening of an office at 412 Beacon Street, Boston, Massachusetts.

\* \* \*

Dr. Frank F. Furstenberg and Dr. Nachman Davidson announce their association for the practice of allergy at 401 Medical Arts Building, Baltimore 1, Maryland.

\* \* \*

Dr. George A. Dean has recently been released from military service and announces his return to private practice at 11 West Church Street, Fairport, New York.

\* \* \*

"Academy News and Notes" published by the American Academy of Pediatrics shows in its treasury report that \$17,348.52 was spent for postwar planning.

\* \* \*

Clifford H. Kalb, M.D., announces the opening of his office, Suite 4115 Plankinton Building, 161 W. Wisconsin Avenue, Milwaukee 3, Wisconsin. His practice is limited to clinical allergy.

\* \* \*

Sylvia Ruby, M.D., announces her release from the United States Navy and her return to the practice of allergy at 270 Commonwealth Avenue, Boston, Massachusetts.

Dr. Rollin M. Perkins has returned from military service and has resumed the practice of allergy at his former address, 1005 First National Bank Building, Davenport, Iowa.

\* \* \*

Jack A. Rudolph, M.D., has recently returned from military service and announces his return to practice which is limited exclusively to allergy, asthma, hay fever, hives, and allied allergic conditions. He is located at 350 Lincoln Building, Miami Beach, Florida.

\* \* \*

The annual meeting and twentieth scientific session of the American Heart Association will be held in Atlantic City, New Jersey, on June 6 and 7, 1947. The scientific sessions will take place on June 6 and 7 at the Hotel President which will be headquarters for all meetings.

\* \* \*

Dr. Harold O. Schneider, formerly associated with the Salem Clinic, Salem, Oregon, has now opened his office at 707-708 First National Bank Building, Salem, Oregon. His practice is limited to internal medicine and allergy. He is eager to obtain a trained technician in allergy. Anyone interested please write Doctor Schneider.

\* \* \*

The American Association of Immunologists will hold its thirty-first annual meeting with the Federation of American Societies for Experimental Biology in Chicago on May 19 and 20, 1947. Registration will open at 9:00 a.m. on Sunday, May 18, at the Stevens Hotel. The registration fee will be \$3.00. All functions will be centralized in the Stevens and Congress Hotels.

According to an announcement in the January, 1947, issue of *The Journal of Allergy*, 144 new members were elected to the American Academy of Allergy at the third annual meeting in New York City. Of this group fifty-nine (41 per cent) are already members of the College. Of seven members elected to Fellowship, two are also Fellows of the College. The American Academy of Allergy, now representing an amalgamation of the American Association for the Study of Allergy and the Society for the Study of Asthma, has a total of 512 Fellows and members. The American College of Allergists now has a total of 654 members.

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### Progress in Allergy

(Continued from Page 88)

86. Swihart, L. F.: Upper respiratory infections in children with special reference to involvement of lymphoid tissue. *J. Indiana M.A.*, 38: 448, 1945.
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# BOOK REVIEWS

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**THE ELECTROCARDIOGRAM—ITS INTERPRETATION AND CLINICAL APPLICATION.** By Louis H. Sigler, M.D. 403 pages. 25 chapters. 203 illus. Price, \$7.50. New York: Grune and Stratton, 1944.

Because there are many books published on the use and interpretation of the electrocardiogram, only the appearance of such a text profusely illustrating every phase of the subject and containing simple and understandable original schematic drawings is justified. The author, with an extensive consultant practice of twenty years, has made a simplified, comprehensive and thorough analysis of the electrocardiogram and its practical application. There are about 400 electrocardiograms with over 1,400 individual lead strips and original schematic drawings.

Emphasis is placed on the essentials with a broad presentation of the theoretical points and the objective findings.

Separate chapters deal with the frequent and the more unusual cardiac arrhythmias, the tachycardias, the bradycardias, and auriculoventricular and bundle branch block.

The elements of physics and electricity relating to electrocardiography are concisely illustrated in many striking diagrams used by the author for many years when teaching the subject. Trauma of the heart and the six precordial leads are covered unusually adequately.

The cardiologist, as well as the internist, will find this book a useful addition to his library.

F.W.W.

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**THE DIAGNOSIS AND TREATMENT OF BRONCHIAL ASTHMA.** By Leslie V. Gay, M.D., with foreword by Warfield T. Longcope, M.D. 119 tables and figures. 334 pages. Price \$5.00. Baltimore: Williams & Wilkins Co., 1946.

This book deals with the author's long experience in the field of asthma. The book is of moderate size and necessarily does not attempt to cover all parts of the subject. There are chapters on the physiology of normal respiration and on the etiology, pathology, diagnosis, differential diagnosis, complications, and treatment of asthma.

The chapter on pathology deals with the autopsy findings in twenty-four asthmatic patients. Each case is given in detail, and the tables and conclusions are well done. Special attention, more than usual in books of this size, is used for the psychoso-

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## BOOK REVIEWS

matic aspects of asthma. The author also deals extensively with the use of radium for adenoid tissue, and with other subjects in which he is particularly interested.

One is necessarily struck with the detail into which the author goes in dealing with the rôle of helium and the use of potassium salts, to mention two. Discussion of these relatively unimportant phases of the subject consumes too many pages, pages which could better have been devoted to more information regarding the source of some of the more important causes of bronchial asthma and to a more explicit discussion of avoidance of these allergens, especially house dust.

The author apparently does not think that foods are important and gives little attention to that phase of the subject. Most allergists believe that inhalant allergens are more important causes of asthma than are foods, but almost all feel that foods frequently cause attacks. There is a good section on the relationship of asthma to the nose and sinuses, but many workers in this field are not as surgically minded as is the author.

There are other shortcomings. The index is small and the bibliography meager. Solutions for hyposensitization are given in mixtures without regard to pollen seasons.

A glaring fault is a statement to the effect that scratch tests are inaccurate and that the intracutaneous method should alone be used. Some similarly minded allergists have found to their chagrin that there is no safety in intradermal testing unless these have been preceded by negative scratch tests. Every fatality or near fatality is an indictment of the few who refuse to do scratch tests. Both the scratch and the intradermal methods make for a safer and a more complete diagnostic survey. Swineford (*Journal of Allergy*, 17:24, 1946) is quite correct when he concludes that "every intradermal test should be preceded by the less sensitive scratch test." Any other technique is dangerous. The medical students and physicians who read this book would do well to bear this in mind.

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# ANNALS *of* ALLERGY

*Published by the  
American College of Allergists*

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Volume 5

March-April, 1947

Number 2

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## SYMPATHECTOMY AS AN ANTIALLERGIC MEASURE

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**M**Y purpose in returning to this subject is not merely to report a few additional experiences in it that strengthen the preliminary impressions of the antiallergic influences of sympathectomy,<sup>1</sup> but also to assemble the data with other related observations in what appears to me to be instructive juxtaposition.

I begin, then, with two case histories, both of which illustrate on the one hand the nonselective, quantitative, antiallergic action of histamine injections, and on the other hand the astonishing, selective, antiallergic action of sympathectomy.

Both of these patients (A.F.C. and C.T.) were nonreaginically sensitive to many foods. Their detailed clinical and dietary histories are reported in the second edition of my monograph.<sup>2</sup>

Table I, a and b, lists the food-allergens of A.F.C. in approximately the chronological order in which they were recognized as excitants or were finally eliminated from the diet after more or less successful attempts to eat them at increasing intervals of time. The three items in bold type in the last column of Table Ia are those that were the last to show themselves as allergens in this case through the appearance of marked allergic symptoms (gastric pain, gas, dizziness). Hence they are rated as the weakest allergens of the list. This conclusion was supported by the observation that the injection of histamine diphosphate in a daily quantity of about 0.1 mg. enabled the patient again to eat those three foods (but not others) without the slightest allergic reaction, although he was still unable to eat oats, corn or spinach (the only other foods tested). The antiallergic effect of the injections of histamine in this case is thus seen to be a weak one and, so far as the tests went, it seemed to be nonselective.

# SYMPATHECTOMY—COCA

TABLE I. PATIENT A. F. C.

A. Nonselective abolishment of the sensitivities to the three weak food-allergens under daily injections of histamine diphosphate. The items in bold type could be eaten without allergic reaction during the period of the injections.

wheat	rice	potato	<b>MILK</b>
<b>pork</b>	<b>oat</b>	<b>peach-plum</b>	<b>FOWL</b>
<b>lemon</b>	<b>tomato</b>	<b>fish</b>	<b>BANANA</b>
<b>CORN</b>	lettuce	onion	
sugar cane	cabbage (fam.)	spinach	
sweet potato	chocolate	carrot	
apple	orange	beet	
	pea-bean	grapefruit	
	peanut	egg	

B. Selective abolishment of food-sensitivities through sympathectomy. The items in bold type have been eaten without allergic reaction since the operation.

wheat	rice	potato	milk
<b>PORK</b>	<b>oat</b>	<b>peach-plum</b>	<b>FOWL</b>
<b>lemon</b>	<b>TOMATO</b>	<b>FISH</b>	<b>BANANA</b>
<b>CORN</b>	lettuce	<b>ONION</b>	
sweet potato	cabbage (fam.)	spinach	
apple	<b>CHOCOLATE</b>	carrot	
<b>SUGAR CANE</b>	orange	beet	
	<b>PEA-BEAN</b>	grapefruit	
	<b>PEANUT</b>	<b>EGG</b>	

Note: These food-allergens are arranged in groups in the order of their recognition as excitants and/or their elimination from the diet.

It may facilitate this discussion to review the matter of the major and minor allergens upon which the present consideration hinges.

Allergens have been designated<sup>2,3</sup> by the relative terms, major and minor, in accordance with two phenomena: (1) As long as the major allergens are being eaten, the minor ones can be eaten without any or with only slight reaction (nonspecific protection through the presumably stronger reaction to the major allergens). (2) A minor allergen can be eaten *once* without reaction, at intervals, varying in different persons, and with the degree of sensitivity, from several days to one or two weeks.

The relative severity of the reaction alone cannot serve as a criterion of distinction of the major from the minor allergens because, in the absence of protection from major allergens, minor allergens *can* cause allergic symptoms quite as severe as those following the ingestion of major allergens.

A number of my patients have, for years, been taking advantage of the second phenomenon (latent period) to extend their restricted list of "safe" foods. On the other hand, their indulgence, even once, in one of their major allergens has always been promptly punished by immediate symptoms and tachycardia.

The items in bold type in Table Ib are those that the patient has been able to eat without any restriction and without the slightest allergic reaction since his sympathectomy. The significant features of this table are:

1. Sensitivity was completely abolished for some of the major allergens (pork, sugar cane, and corn).

2. Sensitivity was not abolished for the *weak* allergen (milk).

It should be emphasized, moreover, that the foods mentioned in the

# SYMPATHECTOMY—COCA

TABLE II. PATIENT C. T.

A. Nonselective abolishment of the sensitivities to the entire "minor" group of allergens and to one of the "medium" group under daily injections of histamine diphosphate. The items in bold type could be eaten without allergic reaction.

<u>Group 1</u> <u>Major</u>	<u>Group 2</u> <u>Medium</u>	<u>Group 3</u> <u>Minor</u>
beef wheat orange grapefruit lemon plum	<b>TOMATO</b> rice rye corn oat coffee onion	<b>SUGAR CANE</b> <b>POTATO</b> <b>BANANA</b> <b>STRAWBERRY</b> <b>ALUMINUM</b>

B. Selective abolishment of food sensitivities, with sympathectomy. The items in bold type have been eaten without allergic reaction ever since the operation.

<u>Group 1</u> <u>Major</u>	<u>Group 2</u> <u>Medium</u>	<u>Group 3</u> <u>Minor</u>
<b>BEEF</b> <b>WHEAT</b> orange grapefruit lemon <b>PLUM</b>	tomato <b>RICE</b> <b>RYE</b> <b>CORN</b> <b>OAT</b> coffee <b>ONION</b>	<b>SUGAR CANE</b> potato <b>BANANA</b> <b>STRAWBERRY</b> <b>ALUMINUM</b> Tobacco Chlorinated water

Note: The sensitivity to tomato and potato, which had been suppressed by histamine injections, remained unaffected by sympathectomy.

first column were those first recognized as allergens in this patient, that the allergic symptoms were severe—headache (often unilateral), nausea, vomiting, gastrointestinal bleeding, dizziness, cramplike gastric pain—and also that all of the other items could at first be eaten once at intervals varying from one to two weeks.

It is seen, then, that in this case the antiallergic effect of the injected histamine is weak and nonselective and presumably represents an increased tolerance of the allergic shock tissues for the allergic H-substance; whereas, on the contrary, section of the sympathetic chain *did not cause any increased nonspecific tolerance for the H-substance*—witness the persistence of the sensitivity to one of the weakest allergens (milk) in this patient.

Thus the antiallergic effect of sympathectomy is revealed as an inexplicably selective one, a phenomenon that invites the attention of the immunologist as well as the neurophysiologist. This phenomenon is exactly duplicated in the records of patient C. T., the salient data of which are presented in Table II, a and b.

In this case, the second (medium) group of food-allergens emerged at different intervals (months) after the major group had been identified, and the minor group made its appearance more than one year after the major group had been eliminated. The chief symptoms were dizziness, "neurasthenia" (suicidal), and abnormal tiredness.

Here also one sees the weak, nonselective tolerance resulting from injections of histamine and the selective and absolute antiallergic effect of sympathectomy.

A later development in this case contributes additional evidence of the

selective quality of the antiallergic action of sympathectomy. Previous to the operation, the patient had eaten fowl with never a consequent allergic symptom nor tachycardia. Since the sympathectomy, fowl causes both tachycardia and allergic symptoms. Sensitivity, to even the weakest of all her allergens, has not been affected by the operation.

In the succeeding four and one-half years no relapses have occurred in the five patients so treated.

Two additional patients have been sufficiently studied to provide useful information, which I shall report now.

The first patient (B. S.), a boy of ten years, suffered from stammering, with marked tic, headaches, asthmatic bronchitis, abnormal tiredness and irritability—a "problem child," according to his parents. It was believed that the stammering was particularly marked after eating of beef, egg, or peas.

The pulse-dietary examination having failed, in several weeks of effort, to disclose any foods that did not excite tachycardia, limited sympathectomy was advised and was performed by Dr. Max Danzis on July 17, 1945. After the wound was quite healed, the dietary diagnosis was resumed and the following pulse-accelerating foods were identified: wheat, oat, orange, pea, bean, peanut, sweet potato and squash-melon family.

Interpretations of the pulse record were made uncommonly difficult by sensitivities to several practically unavoidable inhalant allergens (tobacco- and leaf-smoke and paint-fumes—pulse rates up to 104), which, however, have not caused any frank allergic symptoms, aside from occasional abnormal fatigue. His father writes:

"So long as he avoids the restricted foods, he is free from all the symptoms listed and his disposition has especially improved so that he has become a normally reacting and manageable boy. This latter result is most gratifying to us. . . . Some time ago, for a period of about two weeks, he tried abandoning the dietary restrictions, but with disastrous results; all his symptoms recurred, and at last he voluntarily returned to his nonallergenic diet, and his condition has been most satisfactory since that time."

It would be negligent of me not to dwell, for a moment at least, upon the startling implications of one feature of the case just described. I mean the remarkable change in the disposition and personality of the boy following the correction of his food allergy. Here is a problem child whose behavior toward his parents and his associates was becoming a matter of serious concern, and who, through the mere correction of a purely physiological handicap, has been restored to normal self-control. But, much more than that, the causal relationship of the abnormal behavior and the food allergy has been experimentally demonstrated through the consequences of the boy's deliberate return to his food-allergens. This case suggests the application of the pulse-dietary method with preliminary statistical survey to the study of juvenile delinquency and to criminology in general.

For the peace of mind of some who may balk at my apparent reliance upon a single case—however it may be fortified by experiment—I must refer also to four similarly attested instances of "uncontrollable"

irritability in adults, which was entirely eradicated by mere avoidance of all pulse-accelerating food-allergens, but in these cases without sympathectomy.

One of my associates has raised the question of the nature of the irritability, or, better expressed perhaps, its immediate cause. Two explanations may be considered: (1) The irritability represents merely a normal if somewhat exaggerated reaction to a displeasing situation that is aggravated by existing allergic symptoms (headache, indigestion, et cetera). (2) The irritability is a symptom of food allergy caused by a particular cerebral localization of the allergic reaction and, therefore, is independent of all other symptoms.

This question might be settled at once if marked allergic irritability should be observed in the absence of other recognized food-allergic symptoms, but, unhappily, the occurrence of only one symptom in an allergic person is not common (found in about 3 per cent of all subjects). However, the phenomenon, being itself unusual—only five instances among more than one hundred allergic persons—evidently does not affect many even of those patients who suffer severely from such presumably irritating symptoms as headache, heartburn and abnormal tiredness. Thus, the irritability is not only not a normal reaction; it is even far from usual. Moreover, the affected persons themselves have recognized their irritability as abnormal—they call it “uncontrollable.”

One of these four abnormally irritable patients, previous to the correction of her allergy (pork, wheat), frequently and seriously referred to her uncontrollable “snappishness” as a proper ground for her divorce by her husband and for the loss of her position; whereas she states that after she began to avoid her two pulse-accelerating allergens, six years ago, she has lost the *capacity* to become irritated.

The first explanation that was considered above is one of the commonest fallacies in the field of allergic disease. Perhaps the favorite among these is ascribing a headache to constipation, both of them being demonstrably independent allergic symptoms (among a group of thirty-eight food-allergic patients, there were twenty-five with headache without constipation, four with constipation without headache and nine with both symptoms).

The anatomically separate cerebral localization of some allergic lesions is clearly indicated in the instance of stammering with tic and in those cases of idiopathic epilepsy that have been cured with the use of the pulse-dietary method. With these examples in mind, it should seem reasonable to watch for the possibility of other localizations in such obscure conditions as dementia precox, amnesia, et cetera.

The second new case is noteworthy because it afforded the first opportunity that I have had to observe the temporary effect of ganglion block as an antiallergic measure. This procedure has often been used for the purpose of determining in advance of sympathectomy what thera-

# SYMPATHECTOMY—COCA

TABLE III. PATIENT E. C. PULSE-DIET RECORD

THE ANTIALLERGIC EFFECT OF STELLATE GANGLION BLOCK

Date, 1946	September 27 Pulse	September 28 Pulse	October 4 Pulse	October 5 Pulse
Before Rising—	67	66		69
Before Breakfast	92	81	80	81
30'	92	91	..	81
60'	92	82	..	80
90'	88	83	..	77
Diet—	Oatmeal	Eggs	84	Eggs, toast, butter, coffee
Mid-morning—	89	..	1:30 ganglion- block	77
30'	92	..	..	77
60'	89	..	..	75
90'	91	..	..	74
Diet—	Milk		..	Tomato
Lunch—	85	85	83—2:30	74
30'	86	87	75	77
60'	81	86	76	80
90'	80	87	75	79
Diet—	Eggs (3)	Rice	1 quart of milk— 2:30	Bread, milk, beef, carrot, peas
Mid-afternoon—	80	87	76	79
30'	84	86	77	79
60'	81	85	76	..
90'	..	83	78	76
Diet—	Grapes	Milk	Chicken—6:30	Orange
Dinner—	82	80	77	73
30'	81	87	81	76
60'	81	90	81	73
90'	78	90	..	75
Diet—	Chicken	Chicken, rice, bread, butter	Bread, butter, milk, cane sugar—9:00	Lamb, peas, corn bread, spinach, coffee

peutic effect could be expected from that operation in the particular case. The single criterion of a favorable result in the cases reported by Miscall and Rovenstine was the disappearance of the intractable bronchial asthma, which had resisted all other usually employed modes of treatment in the seventy-two cases composing the total clinical material. The result of the procaine stellate block was favorable in twenty-one of those cases, and the subsequent sympathectomy in the twenty-one patients conferred permanent relief from asthma upon all of them.

Patient E. C., aged fifty-four had suffered for some years from a severe, chronic, nonseasonal conjunctivitis. There had been one attack of retinal edema. The consensus of his physicians had been that the conjunctivitis was allergic, and two experienced allergists had obtained "many positive cutaneous reactions" with the usual tests. No noticeable improvement followed the institution of an anti-allergic regime based on the results of the cutaneous tests.

Table III presents the pulse-dietary record of E. C. for the first two days of the trial diet and for the day of the block, October 4, and the following day. With a low count of 66-67 and an estimated normal high count of 80 or possibly less, the results of the trials on the first two days made it seem unlikely that a nonallergenic diet could be discovered in a reasonable time without the aid of sympathectomy. Since the continuation of the trial diet on September 29 and 30 brought only further discouragement (pulse rates from 81 to 90), the patient

agreed to try the preliminary ganglion block with procaine, which was performed on October 4, by Dr. Rovenstine.

The antiallergic effect of the block was prompt and highly gratifying, inasmuch as it gave reason to anticipate that the operation would enable the patient to eat at least eighteen foods which together contain all the essential nutritional elements.

After the mid-day meal of October 6, (about forty-eight hours after the establishment of the block) the pulse rose suddenly to 88 and remained usually above the estimated normal high point (81) in the next four days. At that time (October 11) a second ganglion block was performed, this time with procaine followed by alcohol (3 c.c.). Again the general pulse level fell but not so suddenly as at the first block. One may consider the question whether such a small residual acceleration of the pulse could have been caused by the tissue-damage following the injection of alcohol. On the second day, the pulse reached 84 once; on the third day it did not pass the normal high of 81. However, on the fifth day and thereafter an antiallergic effect of the block upon the pulse was no longer perceptible, although the physiologic effect of it (dry skin, ptosis) persisted for a few days.

The selectivity of the antiallergic action of the ganglion block was seen in the tests with cigarette smoke. Three such tests were made. In the first, carried out before the blocks, the pulse rate rose from 85 to 119 in 5 minutes. In the second and third tests, which were done in the periods of the first and second block, the rate rose 30 beats within a few minutes. In a number of nonsensitive persons the pulse rate has not been noticeably affected by the smoking of cigarettes.

I have previously noted the fact that no instance of sensitivity to an inhaled allergic excitant, having been abolished by sympathectomy, has yet been observed. Another situation in which the outcome of the operation may be disappointing is the following. If an allergic person is found to be sensitive by the criterion of specific tachycardia to only a few foods, he should be advised not to resort to sympathectomy without first making the ganglion-block test with procaine.

That test is especially desirable in a patient sensitive to only a few foods because of the specificity of the result. The few allergenic foods may by chance not be included in the list of those subject to the selective influence of the operation.

From the above-described experience with alcohol, it would seem that procaine alone should be preferred for the test.

The tissue damage resulting from even the least extensive but effective sympathectomy may cause a disturbingly prolonged tachycardia which, while it lasts, can at first entirely prevent and later interfere seriously with the pulse-dietary study.

In one eleven-year-old girl, for example, the operation occurred in October 27, 1943; the subsequently established normal waking-pulse of 64 was first observed on November 28.

In some patients requiring sympathectomy, where the speedy identification of a sustaining nonallergic diet is urgently demanded, as was the case in E. C., the procaine ganglion-block without alcohol, repeated if necessary after, say, thirty-six to forty-eight hours, provided the key to that emergency.

*(Continued on Page 159)*



## ALLERGIC REACTIONS FROM HANDLING PENICILLIN

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PENICILLIN has met with so much approval by the medical profession and the public that it is frequently called the "magic medicine." The literature is filled with results obtained from its administration in nearly every known medical and surgical condition. There is also a great deal reported in regard to the reactions encountered in its use. It is known to cause allergic reactions of various types in from 5 to 10 per cent of those who use the drug therapeutically. This type of reaction is *not* being discussed in this paper, but there is still another group of people who are made ill merely by handling the drug. This group is composed mainly of doctors, nurses and laboratory workers. Many of these people have never received penicillin as a therapeutic agent, and yet are incapacitated by contact with the material.

Pyle and Rattner, in July, 1944, reported the first cases of "Contact Dermatitis from Penicillin." One was a medical officer in charge of preparing and administering penicillin who developed a mild blepharitis, conjunctivitis and blurring of vision. This developed into an acute dermatitis of nose, forehead and cheeks; then eczematous lesions appeared on the hands and distal portion of the penis. All contact with penicillin was discontinued, and in course of time the lesions healed. Later, penicillin was handled again and lesions promptly appeared in the same areas.

Patch tests were made of materials handled and erythematovesicular reactions occurred.

These same authors reported that three hospital corpsmen also developed erythema of face and penis, but no dermatitis. All of these men gave a negative history of eczema or any previous allergic condition.

Several months later Binkley and Brockmole reported two cases of a dermatitis in a physician after handling the drug.

In analyzing the cases reported in the literature, and the two I have had the opportunity to observe, there is found a wide variety of symptoms. The most frequent symptom present was itching of the skin of the face, neck, and body, areas that had not been in direct contact with the drug. Erythema (redness and itching) was the second most common symptom, and vesiculation was third. It is interesting to note that only two had any involvement of the hands; this is probably explained by frequent washings of the parts.

An analysis of the symptoms of the nine cases reported in the literature and my two additions bring forth the following observations:

1. Itching of skin in other areas—face, neck, body (indirect contact): ten cases (91 per cent). This is particularly interesting in that distant areas are so susceptible.
2. Erythema (generalized): eight cases (73 per cent).

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Read before the American College of Allergists, San Francisco, California, June 28 to 30, 1946.

3. Vesicles and/or papules: seven cases (64 per cent).
4. Involvement distal third of penis: five cases (45 per cent).
5. Edema of eyelids: four cases (36 per cent).
6. Itching of hands (direct contact) only: two cases (18 per cent). This was probably due to frequent washing.
7. Whealing: two cases (18 per cent).
8. Conjunctivitis: two cases (18 per cent).
9. Nasal congestion: two cases (18 per cent).
10. Vesicles or erythema: one case (9 per cent).
11. Desquamation: one case (9 per cent).
12. Blepharitis: one case (9 per cent).
13. Blurring of vision: one case (9 per cent).
14. Photophobia: one case (9 per cent).

The time interval seems to vary widely. Some cases resulted within twenty-four hours after handling the drug, while others were delayed as long as *seven months* before any evidence of sensitivity was noted.

There is no possible way to determine the percentage of handlers who have developed some form of allergic reaction to penicillin. The total number of handlers is enormous and the reported cases of reactions are exceedingly small, thus the writer deduces that the figure is less than 1 per cent.

To this small number of cases of contact dermatitis due to handling penicillin, the author wishes to add two others who developed allergic symptoms other than dermatitis. These two patients developed urticaria with frank whealing. One girl had nasal congestion when the itching and whealing began, the other when in the room where penicillin was being prepared, even though she was not handling the drug. Photophobia occurred in the second patient, and was associated with conjunctivitis and edema of the eyelids. Neither of these patients had a contact dermatitis as noted in the other cases. Both of these were nurses working in general hospitals.

#### CASE REPORTS

*Case 1.*—Mrs. T., aged thirty-eight, had a Caesarean section in April, 1945. She was given sulfa drugs, and developed an itching and a swelling of her fingers and feet for two to three days. In September, 1945, she had an appendectomy, received no sulfa or penicillin, and had an uneventful recovery. In December, 1945, a herniorrhaphy was done, after which peritonitis developed. She was given sulfa and penicillin, and had a generalized urticaria following them. In February, 1946, two months later, she began working in the same hospital, and forty-eight hours after handling sulfa and penicillin, she began itching over her entire body and developed wheals on her legs only. This persisted for ten days. When I saw her, she was fairly comfortable for the first time because she had not been on duty for eighteen hours. Sulfa and penicillin were applied to the unbroken skin, and the penicillin area turned pink and itched. Scratch tests to both were made, and the sulfa was negative, while penicillin gave a definitely positive reaction with pseudopods. Endermal tests to penicillin spores were negative.

Six weeks later, the patient reported that every time she entered the room where penicillin was being prepared, her nose immediately became congested. This was relieved shortly after leaving the room.

*Case 2.*—Miss C., aged twenty-six, also a nurse, had never received penicillin therapy. She gave no history of eczema or allergy. She had administered a few doses of penicillin over a period of months. Then she began handling it almost constantly, and twenty-four hours later, redness, itching, whealing and a fine papular rash appeared on her face and arms. She discontinued the contact, and three weeks later was completely cured. Recovery was slow because she still handled the drug one day a week for three weeks. One month later she started handling the drug again, and in less than twenty-four hours her eyelids were swollen almost shut, and redness of face and a fine rash on her arms appeared. This cleared in one week after discontinuing contact with the drug. Each contact had caused photophobia, and some congestion of the nose, both of which disappeared soon after cessation of handling the drug.

Placing a drop of penicillin solution on her arm caused redness and itching within six hours. No scratch tests were made, and she was not tested for penicillin spores.

Everyone agrees that the only treatment is avoidance of the drug. The contact dermatitis and urticaria heal spontaneously if given a chance. I am attempting to desensitize my first patient by giving small doses of a very weak solution of penicillin, but it is too early to make any comments on the results.

## SUMMARY

A review of the literature indicates that penicillin causes various allergic reactions such as contact dermatitis, urticaria and vasomotor rhinitis in a very small percentage of the people who handle it.

Urticaria, photophobia and nasal congestion are reported for the first time as a result of contact with the drug.

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## PENICILLIN CREAM

In view of the increasing reports of penicillin sensitivity, a possible commercial source of clinical significance may be a penicillin (200 units per gm.) cream for sycosis barbae, the successful use of which has been reported in the *British Journal of Dermatology and Syphilis* (May-June, 1945).

# THE USE OF BENADRYL IN THE TREATMENT OF CERTAIN ALLERGIC DISEASES OF CHILDREN

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NEARLY a year ago benadryl (beta dimethylaminoethyl benzhydryl ether hydrochloride)<sup>†</sup> became available to members of the section on pediatrics of the Mayo Clinic for clinical trial in the treatment of the allergic diseases of children. This report concerns our experiences with its therapeutic use against asthma, hay fever, vasomotor rhinitis and urticaria. The results of treating seventy-one children form the basis of this report. All of the cases included in a preliminary report<sup>5</sup> have been included in this study also because further observations have been made concerning the treatment in some of them.

## DOSE AND ADMINISTRATION

The determination of an effective dose of any new drug for children of various ages is important. A summary of the daily doses employed in treating this group of seventy-one children is given in Table I. In all instances the results were satisfactory unless otherwise noted. It was found that for the four allergic diseases being studied, the severity of the disease rather than the type of disease determined the size of the dose of benadryl needed for children of the same age.

The frequency of administration depended on the duration of effect. Single doses were in some instances adequate. The duration of the beneficial effect has varied from ninety minutes to nearly twenty-four hours. In severe cases the dose may have to be repeated every one to two hours for several doses. In most instances in this group of children, the drug was given two to five times in twenty-four hours.

When the total daily doses were compared with the weights of the children, it was found that the dose varied from 0.5 to 6 mg. per pound (1 to 12 mg. per kilogram). The higher dose slightly exceeds the value of 5 mg. per pound (10 mg. per kilogram) which was found by one group of investigators<sup>9</sup> to be the largest single dose which can be safely administered to dogs. However, others<sup>10</sup> have safely used as much as 8 mg. per pound (16 mg. per kilogram) for dogs. The latter authors, however, have found that 5 mg. per pound (10 mg. per kilogram) of benadryl produces in dogs nearly maximal histamine antagonism. Loew and his co-workers<sup>4</sup> found that 5 mg. per pound (10 mg. per kilogram) may be safely given to dogs in a 5 per cent solution subcutaneously. This dose represented a half to a third of the quantity necessary to produce excitation and tremors.

Read at the meeting of the American College of Allergists, San Francisco, California, June 28 to 30, 1946.

<sup>†</sup>The benadryl used in the study was supplied by Parke, Davis and Company.

TABLE I. RESULTS OF TREATING SEVENTY-ONE CHILDREN WITH BENADRYL

Age, yrs.	Daily dose, mg.	Cases	Remarks
$\frac{3}{4}$	10-30	3	
1	10-120	5	10 mg. ineffective in 1 case of urticaria
2	10-60	7	60 mg. ineffective in 1 case of asthma
3	20-170	9	20 mg. ineffective in 1 case of urticaria
4	12.5-150	4	80-150 mg. gave only fair results in 2 cases of asthma
5	25-150	7	150 mg. gave only fairly good results in 1 case of vasomotor rhinitis
6	25-200	2	
7	25-300	4	
8	50-200	4	
9	150-250	4	
10	50-100	4	100 mg. ineffective in 1 case of hay fever
11	150	2	
12	100-200	6	100 mg. ineffective in 1 case of vasomotor rhinitis
13	50-200	3	200 mg. ineffective in 1 case of chronic asthma
14	50-450	7	450 mg. ineffective in 1 case of angioneurotic edema

The lethal dose of benadryl varies for different species of animals.<sup>9</sup> Therefore, the results of treating dogs cannot be used entirely in determining the human dose. Experience of my colleagues and myself so far indicates that at least 6 mg. per pound (12 mg. per kilogram) in a twenty-four hour period can be given safely to many children. We have not administered this large dose for more than one day. A daily dose of 2 mg. per pound (4 mg. per kilogram) is frequently effective.

For prompt action, benadryl is best given when the stomach is empty. When a chronic disease, such as vasomotor rhinitis, is being treated, prompt action is not important. Its use then after meals will avoid the nausea which occasionally follows its ingestion before meals. The length of time during which benadryl can be continuously administered safely has not been determined. Among adults, eleven months is the longest time an individual has taken the drug.<sup>7</sup> In this group of children, one child has taken the drug daily for nine months, but none of the others has taken it for longer than a few weeks at a time though some have had repeated courses.

No ill effects have been noted during the prolonged, although usually intermittent, administration, nor has an increasing tolerance been noted. In three cases in which intermittent treatment was given, a slightly larger

dose was necessary during later attacks. This may have been due to the greater severity of the later attacks.

TABLE II. REACTIONS TO TREATMENT  
OF SEVENTY-ONE CHILDREN WITH  
BENADRYL  
(Nineteen reactions among seventeen  
children)

Reaction	Children affected
Drowsiness	10
Vomiting	3
Diarrhea	1
Nausea	1
Headache	1
"Crabby"	1
Tachycardia	1
Hematuria	1

#### UNDESIRABLE REACTIONS

Undesirable reactions have been noted by seventeen of the seventy-one patients, an incidence of approximately 24 per cent. The reactions necessitated stopping the use of the drug by six children. These reactions are summarized in Table II. Three of the children who were made drowsy discontinued use of benadryl on that account. Two others noted drowsiness after the first few doses but none after that. One boy simply stopped its use during the daytime but continued to take a dose at bedtime. Another cut down the amount used during the daytime and increased the dose taken at night. One boy became both nauseated and drowsy from the first dose. The nausea stopped when the drug was given after instead of before meals. Two of the episodes of vomiting probably were not due to benadryl but occurred during treatment or immediately after the medication was stopped for one child who was being treated for hay fever and for another who had vasomotor rhinitis. In the third case in which vomiting occurred diarrhea also was noted. The patient was an infant nine months old. The vomiting followed several hours after the ingestion of 10 mg. of benadryl in elixir form. A three-year-old boy had a headache which came on fifteen minutes after ingestion of the drug and lasted an hour. The asthmatic relief afforded by the benadryl was great enough so that its use was not discontinued. The headaches were not experienced when later attacks of asthma were treated with benadryl. The "crabby" reaction is a hard one to evaluate. It was a complaint made by the mother during the four days one of the nine-year-old boys took the drug.

Hematuria was noted within twelve hours after the administration of 4 ounces of the elixir (320 mg. of benadryl) to a three-year-old boy in a period of three days. The first pink urine passed by the boy was not

available for examination. The next specimen contained red blood cells, graded 3 (three-fourths of the high-power field was filled with cells). Another specimen obtained twenty-four hours later was free of blood. The boy has not been given more benadryl.

TABLE III. RESULTS OF TREATING  
TWENTY-FOUR CHILDREN WITH  
BENADRYL  
(Asthma)

Age of patients Daily dose, mg.	Asthma	
	9 mos. to 13 yrs. 10-300	
Results	Single attack	Multiple attack
Good	5	11
Fair	1	5
No effect	1	1

Other undesirable reactions noted by adults are dizziness, dry mouth, feeling of nervousness, epigastric distress, and difficulty in co-ordination and dilatation of the pupils.<sup>2,6,8</sup> Still other undesirable reactions may be encountered after more children have been treated. No others have been encountered among the group given benadryl for other diseases than those being reported herein. Leukopenia has not been reported but theoretically might occur. It would seem desirable to perform periodic erythrocyte and leukocyte counts on children who are taking the drug for a prolonged period.

#### COMBINATION OF BENADRYL WITH OTHER DRUGS

Benadryl has been administered before, after and concurrently with such drugs as potassium and sodium iodide, epinephrine, aminophylline and diphenylhydantoin sodium (dilantin) without untoward reaction. Loew and his co-workers,<sup>4</sup> however, have experimentally shown that "adequate doses" of benadryl augment the response to epinephrine. This observation suggests that caution be exercised when this combination is to be employed. The combination of one of the iodides and benadryl has been found to be particularly effective against frequently recurring non-seasonal asthma for patients who did not have extensive pathologic changes in the lung. The iodides are often administered daily and the benadryl is used at the start of any asthmatic episode. This combination makes use of the liquefying action of the iodides on bronchial secretion, and of the bronchodilating<sup>1,3,4</sup> and antihistamine actions of benadryl.<sup>4,10,11</sup>

#### ASTHMA

The results of treating twenty-four children suffering from asthma are summarized in Table III. Twelve of these children had an apparent in-

## BENADRYL IN ALLERGIC DISEASES—LOGAN

fection of the respiratory tract with fever just preceding or accompanying some of their attacks of asthma. In three cases of this group in which single attacks of asthma were treated with benadryl, colds were associated. The results of treatment seemed the same whether the attack was associated with infection or not. In several instances the earlier in the course of the

TABLE IV. RESULTS OF TREATING  
CHILDREN WITH BENADRYL  
(Hay Fever and Vasomotor Rhinitis)

	Hay fever	Vasomotor rhinitis
Age of patients, yrs.	3½-14	2-13
Daily dose, mg.	50-200	40-250
Results:		
Good	10	10
Fair	1	6
Questionable	1	
No effect	1	2
Total cases	13	18

attack the drug was administered, the more prompt and complete was the relief obtained. The one patient among the group treated for a single attack who failed to obtain benefit was a girl, two and a half years old, who had had a few previous bouts of asthma. None had been associated with infection. The child was brought to the clinic for treatment twenty-four hours after the onset. Sixty milligrams of benadryl given orally in two hours did not produce a favorable result. She obtained prompt relief following the subcutaneous administration of 0.3 c.c. of a 1:1,000 aqueous solution of epinephrine hydrochloride. The failure among the seventeen cases in which multiple attacks were treated was in the case of a thirteen-year-old boy who had had chronic asthma for twelve years and also had bronchiectasis. He took 150 mg. of benadryl daily for a month without effect. He was benefited considerably by bronchoscopic aspiration and the subsequent institution of daily treatment with iodide. The effect of benadryl when it was effective was prompt. The effects lasted from ninety minutes to as long as eighteen hours.

### HAY FEVER

Thirteen patients having seasonal hay fever were treated during the fall of 1945. The offending substance was ragweed in most of the cases. Three of these patients had associated asthma. The results of treatment of the hay fever are recorded in Table IV. The results of treatment with benadryl on the associated asthma were good in one case, fair in one and questionable in one. One of the patients who had hay fever and asthma, a fourteen-year-old boy, became slightly drowsy while taking a dose of 50



mg. twice daily. However, the relief he obtained was such that the use of the drug was continued throughout the season. He also has a mild springtime hay fever. The drowsy reaction was again noted when he tried the drug in April, 1946. This time the reaction was more bothersome than the symptoms of hay fever so that he stopped using benadryl.

An episode of vomiting caused stopping of administration of the drug to a nine-year-old girl after eighteen days of administration. However, she had had vomiting episodes during previous attacks of hay fever.

This experience with a small group of children in one season cannot give the answer as to whether the use of benadryl might supplant hypsensitization as the treatment of choice for hay fever. Neither method works in every instance. If further experience with benadryl parallels the early results and if undesirable reactions to its use prove to be no greater than observed to the present time, then the use of benadryl may be a preferred treatment. Preseasonal, coseasonal or perennial hypsensitization treatment can be reserved for those who fail to secure satisfactory results from benadryl. A combination of both methods of treatment may produce the best results in more severe cases.

#### VASOMOTOR RHINITIS

Eighteen children having vasomotor rhinitis have been treated for periods ranging from a few days to nine months. The results are tabulated in Table IV. We were anxious to learn how effective the drug might be against this disease but were hesitant to administer it routinely for long periods. Therefore, the necessary eliminations and home cleanups were advised as the first measure. Benadryl was to be used only if these measures were not possible or failed to produce the desired results. Several parents wrote to us that after adequate cleanups the use of benadryl seemed to them unnecessary and was not tried.

One boy, six years old, had had a stuffy nose most of his life which interfered with his sleep. Neither history nor skin tests disclosed a reason for this. Twenty-five milligrams of benadryl taken at bedtime seemed to improve his nasal airway and permitted his sleeping quietly. He took the drug for three months, stopped for a time and then after an influenza-like infection, when the nasal stuffiness recurred, resumed the same dose with good results. Four children having perennially plugged and running noses needed their tonsils and adenoids removed but the nasal condition constantly seemed to contra-indicate operation. Within a few days after they started to take benadryl, the nasal discharge abated and one to two weeks later the tonsils and adenoids were removed. In each case use of the drug has been stopped postoperatively. Whether its use will be necessary later will be a matter of further observation.

The girl who has taken the drug under our direction for the longest period of time, nine months, is afflicted with cerebral palsy as well as vasomotor rhinitis. Benadryl controlled not only the nasal discharge but also the drooling which has always been troublesome. During the spring

pollen season of 1946, the nasal symptoms were not controlled with 50 mg. twice daily. An increase to 50 mg. three times daily produced satisfactory control.

Children who have had vasomotor rhinitis for several years sometimes

TABLE V. RESULTS OF TREATING SIX-TEEN CHILDREN WITH BENADRYL (Urticaria)\*

	Etiology		
	Miscellaneous	Serum	Penicillin
Cases	10	2	4
Age, yrs.	1-14	3	1-6
Daily doses, mg.	10-450	30-60	30-200
Results:			
Prompt; few doses necessary	7	2	0
Prompt; repeated doses necessary	2	0	3
Fair subjective relief, poor objective relief	0	0	1
No effect	1	0	0

\*One case of angioneurotic edema was included in this group.

do not respond to the treatment with benadryl for several days after it is begun. At times rather large doses have to be employed. One boy, nine years old, failed to experience any relief after taking 150 mg. daily for several days. When the daily dose was increased to 250 mg., he had little nasal discharge and a clear airway. A boy, twelve years old, had a similar experience.

#### URTICARIA

The results of the treatment of urticaria are summarized in Table V. The hives, which were not the result of administration of penicillin, responded promptly for the most part to use of benadryl. Seven of the ten patients had relief of itching in less than twenty minutes. In some, the skin lesions cleared in the same period of time. Prompt administration of the drug seemed to be followed by prompt relief of symptoms. Two of the children securing immediate relief had to be given repeated doses, every three hours for ten to twenty-one days, before the urticaria cleared.

The failure in this group occurred in the case of a fourteen-year-old boy who had recurrent angioneurotic edema involving one arm. This case was included with the cases of urticaria. Fifty milligrams of benadryl, three times daily, gave no relief. Four hundred and fifty milligrams were then given in three hours. This dose made him sleepy but had no effect on the swelling or pain in the arm. Both patients having serum reactions,

one to prophylactic tetanus gas gangrene serum, the other to human plasma, secured good relief when an adequate dose of benadryl was given.

It is hard to know why the four children whose hives seemed to result from penicillin should have required so much benadryl over such a long period of time. One patient, three years of age, took benadryl for seven days. During one period of eighteen hours she needed 170 mg. of the drug in the elixir form. Another child of two and a half years of age took the drug for more than four weeks though it was never necessary to give more than 50 mg. and usually no more than 30 mg. daily to control the urticaria.

Each of the other two patients was treated also with pyribenzamine\* by suppository. One of these, a child one year old, had secured symptomatic relief from 20 mg. of benadryl every four hours, but the other drug gave both symptomatic and objective relief. The other child who was seven years old secured prompt but transient symptomatic relief following each dose of benadryl and objective relief following most of the doses. Pyribenzamine in the dose employed did not give quite as satisfactory a relief and the little girl objected to suppository medication.

#### SUMMARY

Benadryl has been administered to seventy-one children suffering from asthma, hay fever, vasomotor rhinitis or urticaria. Six of seven children treated for single attacks of asthma were considered benefited to some degree and sixteen of seventeen, treated for multiple attacks, also obtained some benefit. Eleven of thirteen children treated for hay fever obtained some benefit as did sixteen of eighteen children treated for vasomotor rhinitis. Fifteen of sixteen children treated for urticaria obtained some degree of benefit. Seventeen of the seventy-one children had as undesirable reactions: drowsiness, vomiting, nausea, headache, crabbiness, tachycardia or hematuria. Administration of the drug to six of the seventeen children was stopped because of the reaction. The doses of the drug employed in treating this group of children ranged from 10 to 450 mg. per day. The results of this study indicate that benadryl in adequate dosage is a valuable addition to the group of drugs used in the symptomatic treatment of allergic diseases in children.

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\*Supplied by Ciba Pharmaceutical Products, Inc.

## ANTIHISTAMINIC SUBSTANCES AND EXPERIMENTAL SENSITIZATIONS

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THE histamine theory of anaphylaxis has lately been generalized and extended to the field of clinical allergy. The symptoms of urticaria, serum disease, hay fever, physical allergies and asthma are considered by many authors to be produced by histamine or a histamine-like substance released during the allergic reaction. The important question, of whether the release of such a substance during anaphylaxis and allergic manifestations is an integral part of these reactions, has not yet been proved. Code<sup>2</sup> attributes to it a secondary role. In agreement with Code's theory, we were inclined to consider that the phenomenology and etiology of allergic dermatitis are independent of the release of histamine or a histamine-like substance. This judgment was based upon several observations: First, dermatitis or inflammation of the skin is not part of the typical histamine pharmacology, contrary to wheals and dilation of the capillaries. Second, the so-called antihistaminic substances, as *pyribenzamine*\* (Mayer, Hutterer and Scholz,<sup>17</sup> Mayer,<sup>11</sup> Mathieson et al,<sup>10</sup> Yonkman et al<sup>22</sup>), 2339 RP (*antergan*)\*\* (Halpern,<sup>4</sup> Halpern and Walther<sup>5</sup>), or *benadryl*\*\*\* (Loew et al<sup>8,9</sup>) have little or no effect in contact dermatitis.

In a previous study, an effort was made to explain this relative inactivity of antihistaminic substances in dermatitis and to elucidate the role of histamine in epidermal reactions to irritants and antigens (Mayer and Brousseau<sup>15</sup>). For this purpose, the influence of pyribenzamine upon primary non-allergic skin reactions in guinea pigs and rabbits, and upon contact dermatitis produced in guinea pigs by sensitization to various chemical substances, was investigated. Results from these experiments showed that pyribenzamine had a definite prophylactic effect upon the first stages of the primary irritation and also upon the experimental sensitizations. It seemed, therefore, that contrary to our former conception, histamine or a histamine-like substance does indeed play an active role in the production of epidermal inflammation, whether it is produced by an irritant or by an antigen.

In the present experiments, the effect of pyribenzamine upon experimental sensitizations was studied in greater detail. The following experiments were performed: (1) Sensitization of guinea pigs with horse serum, representing the typical anaphylaxis in which an increase of histamine in the blood is regularly produced. (2) Sensitization of the

From the Research Laboratories, Ciba Pharmaceutical Products, Inc., Summit, N. J. Presented at the annual meeting of the American College of Allergists, San Francisco, California, June 28 to 30, 1946.

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\*N'-pyridyl-N'-Benzyl-N-dimethyl ethylenediamine monohydrochloride (Ciba)

\*\*Dimethyl-amino-ethyl-benzyl aniline hydrochloride (Specia, Rhone-Poulenc, Paris)

\*\*\*Dimethyl-amino-ethyl-benzhydryl-ether hydrochloride (Parke, Davis & Co.)

# ANTI-HISTAMINIC SUBSTANCES—MAYER

TABLE I. ANAPHYLAXIS IN GUINEA PIGS. SENSITIZATION WITH HORSE SERUM. PROTECTIVE ACTION OF PYRIBENZAMINE BY SUBCUTANEOUS INJECTION.

Pyribenzamine Mg. Per Kg. Body Weight	Number of Animals	Result			
		No Shock	Slight Shock	Heavy Shock	Fatal Shock
0.0 (Controls)	13	0	0	0	13
0.1	5	0	3	0	2
0.5	15	6	3	1	5
1.0	12	5	2	0	5
2.5	2	2	0	0	0
5.	3	3	0	0	0
10.	2	2	0	0	0
20.	2	2	0	0	0

guinea pig skin with hog serum. The manifestations of this sensitization are twofold; an inflammation of the subcutaneous and epidermal layers of the skin at the site of the reinjection of the antigen, and a marked reaction of the vascular system of the papillary body, leading to a morbilliform, almost urticarial rash. (3) Sensitization of the guinea pig skin with chemical substances of low molecular weight, producing a reaction of the epidermal cells representing the contact dermatitis type.

## ACTIVE ANAPHYLAXIS OF GUINEA PIGS

Fifty-four guinea pigs were sensitized against horse serum in the usual manner; two intraperitoneal injections of 0.5 ml. each at forty-eight-hour intervals. Twenty-one days later anaphylactic shock was produced by intracardial injection of 1 ml. of undiluted horse serum. Thirteen animals served as controls; forty-one animals were treated with pyribenzamine in doses varying from 0.1 mg. to 20 mg. per kg. body weight fifteen minutes before the challenging dose of horse serum.

Table I summarizes the results of these experiments. All thirteen control animals which had not received pyribenzamine died from shock within a few minutes after the injection. Animals treated with pyribenzamine in doses as small as 0.1 mg. per kg. body weight were protected against fatal shock. Sixty-three per cent of the twenty-seven animals which had received 0.5 mg. to 1 mg. pyribenzamine per kg. body weight, survived. Of the seventeen surviving animals, only one underwent severe shock, while eleven did not show any signs of shock.

Since the toxic dose of pyribenzamine for guinea pigs by subcutaneous injection is approximately 35 mg. per kg. body weight, the therapeutic index in guinea pig anaphylaxis is about 70 or higher, indicating the minimum therapeutic doses protecting over 50 per cent of the animals.



Fig. 1. Guinea pigs sensitized to hog serum. Animal on the right: Challenged, untreated. Animal on the left: Challenged. Eighteen hours after challenge 1 mg./kg. of pyribenzamine were given subcutaneously. Picture taken fifteen minutes later. Before treatment the erythema was identical to that of the animal on the left.



Similar protection with pyribenzamine has been obtained in passive anaphylaxis of guinea pigs against anti-human rabbit serum by Arbesman, Koepf and Lenzner.<sup>1</sup>

It is interesting to compare the activity of pyribenzamine in anaphylaxis with its activity in histamine poisoning of guinea pigs. The LD<sup>100</sup> of histamine phosphate for guinea pigs by intravenous injection is approximately 0.5 mg. per kg. body weight. Five mg. per kg. body weight of pyribenzamine protects the animals against more than 50 mg. of histamine phosphate (Mayer<sup>11</sup>). This indicates that the smallest dose of pyribenzamine, namely, 0.1 mg., which is active in anaphylactic shock, would protect guinea pigs against 1 mg. of histamine phosphate or against about two lethal doses. Since approximately 0.5 mg. of histamine are liberated during a lethal anaphylactic shock in guinea pigs (Code), one may interpolate that 0.1 mg. of pyribenzamine represents the average limit of protective activity in anaphylaxis.

#### SENSITIZATION OF GUINEA PIGS WITH HOG SERUM

In a previous study it was shown that intradermal or subcutaneous treatment of guinea pigs with hog serum produces a strong sensitization of the skin, in addition to a general sensitization of the anaphylactic type (Jordan and Mayer<sup>6</sup>). Intradermal reinjection of hog serum into sensitized guinea pigs regularly produces a strong local inflammation at the site of the challenging injection with intensive swelling of an area of 1 to 2 inches in diameter, with or without central necrosis. Simultaneously, the site of the preparatory injections flares up and both inflammations persist for several days. In addition to the local reactions, the skin of the ears, nose, eyes and feet becomes reddened and swollen about sixteen hours after the re-injection, and a generalized dermatitis medicamentosa develops, especially on shaven parts of the body. Contrary to the local reactions, this general rash is that of an urticarial type, and a histological examination reveals that the papillary body is primarily affected, with dilation of the blood vessels and lymphatics. The epidermis is almost normal and no cell increase occurs.

Similar local sensitization with rashes was also obtained in guinea pigs sensitized with horse serum (Dienes and Simon<sup>3</sup>), but according to our own experiments, the reactions with hog serum were much more constant and stronger.

In this experiment, twenty guinea pigs were sensitized with two subcutaneous injections of 0.2 ml. each, of undiluted fresh hog serum, and twenty-one days later retested, on the opposite side, with an intradermal injection of 0.1 ml. of undiluted hog serum. The local and flare-up reactions were fully developed within sixteen to twenty hours and remained unchanged for an additional twenty-four hours. Many animals had, at the same time, a generalized rash, as well as deep red ears, swollen eyes and nostrils.



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TABLE II. EFFECT IN GUINEA PIGS OF PYRIBENZAMINE UPON THE VASCULAR SKIN REACTIONS AFTER SENSITIZATION WITH HOG SERUM

Action	Pyribenzamine Doses—Mg. Per Kg.					
	0.1	1	5	10	20	25
	None	None	None in one case, active in another	None in one case, active in three others	Active in three cases	Active in two cases

Sixteen hours after the challenging dose, at the height of the skin reactions, the animals received varying amounts of pyribenzamine subcutaneously. No definite changes were observed with doses of less than 5 mg. per kg. body weight. Doses of 10 to 25 mg., however, were effective, for in about fifteen to thirty-five minutes after the injections, the redness of the ears, eyes and nose disappeared and the generalized rash faded. We also had the impression that, simultaneously, the inflammations of the flare-up reaction and at the site of the reinjection decreased to some extent. After two to five hours the rash and the redness of the ears and nose reappeared, and the inflammations at the injection sites again became as pronounced as before (Table II, Fig. 1).

We believe that this action of pyribenzamine is not a normal pharmacological effect upon the capillaries since this compound does not exercise any direct vasoconstrictor action upon the capillaries or large blood vessels (Smith<sup>10</sup>). The injection of larger doses into animals produces a marked blood pressure fall; thus, the anti-allergic effect of pyribenzamine is, apparently, different from that of epinephrine. One mg. per kg. of epinephrine clears the rash of guinea pigs sensitized to hog serum within a few minutes, and it is quite probable that this action is due, at least to a certain extent, to a direct vasoconstrictor action upon the capillaries of the skin.

We therefore assume that pyribenzamine acts specifically upon the vascular symptoms, upon the rash, and partially upon the inflammation at the site of the reinjection, and in the same way as it does upon the wheals in serum disease or urticaria. In both cases, the skin manifestations disappear twenty to thirty minutes after oral intake of the drug.

If one compares the doses of pyribenzamine which are effective in anaphylactic shock, with those which clear the vascular syndromes in hog serum sensitizations, it is evident that ten to twenty times more pyribenzamine is necessary to treat these skin manifestations than is required to prevent generalized anaphylactic shock. While we have, as yet, no results on the prophylactic effect of pyribenzamine in this type of sensitization, it might well be possible that this difference is due to the fact that it is more difficult to reduce pathological manifestations than to prevent them.

It is concluded from these experiments that pyribenzamine is capable of completely suppressing the specific symptoms of the experimental vascular sensitization of the skin, as it suppresses the specific symptoms of the general sensitization of the vascular system and smooth muscles in anaphylaxis.

#### EPIDERMAL SENSITIZATIONS

A. *Sensitizations to p-phenylenediamine.* Contrary to the previous sensitization of the guinea pig skin with hog serum, the pre-treatment of the guinea pig skin with p-phenylenediamine primarily sensitizes the epidermis, and the challenge with local application of the antigen elicits a reaction of the contact dermatitis type (Mayer<sup>22</sup>). Under normal conditions of occupational sensitization, p-phenylenediamine is one of those interesting substances which produces contact dermatitis, atopic eczema, as well as asthma. In guinea pigs, however, the epidermal layers of the skin are the site of the primary sensitization if the sensitizing substance is introduced into the skin; this allergic manifestation constitutes a true allergy which strictly follows Doerr's criteria. The histological picture is that of a typical dermatitis with intra-epidermal edema and vesicles. In later stages the papillary body and deeper layers of the cutis also become markedly involved.

In order to produce strong sensitizations in a large percentage of the animals, the guinea pigs were sensitized by a daily treatment of the skin for eight consecutive days with an ointment consisting of a 10 per cent p-phenylenediamine suspension in petrolatum. During the entire period of sensitization the animals were kept on a diet slightly deficient in Vitamin C (Mayer and Sulzberger,<sup>18</sup> Sulzberger and Mayer<sup>21</sup>). Twenty-one days after the beginning of this treatment the degree of sensitization was tested by an intradermal test reaction with 0.5 per cent aqueous solution of p-phenylenediamine.

Application of the 10 per cent p-phenylenediamine ointment to undamaged skin of normal guinea pigs does not produce any inflammatory reaction, while sensitized guinea pigs, on the other hand, develop an acute dermatitis with progressive infiltration of the skin, and vesicle formation with crusts, upon a single contact with this ointment. The infiltration regresses slowly with extensive scaling. At the same time, the p-phenylenediamine is rapidly oxidized to quinone-di-imine on the surface of the skin; this highly reactive oxidation product combines particularly with the sulfur-containing cell components and stains the skin black, as it does on furs. The intensity of blackening parallels the intensity of the inflammation and reflects the strongly increased oxidase-content of the skin at the area of reaction.

In these experiments seventy guinea pigs were sensitized, and about one-half of these animals were treated with pyribenzamine, the remainder serving as controls. The antihistaminic substance was administered by two

# ANTI-HISTAMINIC SUBSTANCES—MAYER

TABLE III (A). INFLUENCE OF PYRIBENZAMINE UPON EXPERIMENTAL CONTACT DERMATITIS AFTER SENSITIZATION OF GUINEA PIGS WITH P-PHENYLENEDIAMINE. PROTECTION AFTER SUBCUTANEOUS INJECTION

Number of Animals	Pre-treatment	Pyribenzamine Administered	Animals Showing							
			Dermatitis				Diamine Oxidation			
			++++	++	+	0	++++	++	0	(+)
6	None (Not sensitized)	None				6				6
13	Sensitized	None	5	8			4	9		
15	Sensitized	20 mg./kg.		9	6			7	8	

TABLE III (B). INFLUENCE OF PYRIBENZAMINE UPON EXPERIMENTAL CONTACT DERMATITIS AFTER SENSITIZATION OF GUINEA PIGS WITH P-PHENYLENEDIAMINE. PROTECTION AFTER LOCAL TREATMENT WITH 2 PER CENT PYRIBENZAMINE IN OIL

Number of Animals	Pre-treatment	Pyribenzamine Administered	Animals Showing							
			Dermatitis				Diamine Oxidation			
			++++	++	+	0	++++	++	0	(+)
2	None (Not sensitized)	None				2				2
5	Sensitized	None	5				5			
5	Sensitized	2% Pbz. in oil		1	4			1	4	

routes: by subcutaneous injections, and locally as an oily solution of the base.

*Subcutaneous Injections.* Thirty white guinea pigs weighing from 250 to 300 grams were sensitized to p-phenylenediamine. Marked hypersensitivity developed in twenty-eight of them. These were separated into two groups of thirteen and fifteen animals. The first series served as controls, while the second series was treated with 20 mg. per kg. pyribenzamine. The injections of the antihistaminic substance were started fifteen minutes before retreatment with the antigen, and then repeated three times daily for the following two days.

The control animals showed a strong discoloration of the area challenged with p-phenylenediamine and an intensive dermatitis after twenty-four hours. Both phenomena heightened during the next twenty-four hours. In contrast to the control animals, the dermatitis was less severe and the discoloration of the skin less pronounced in all pyribenzamine-treated animals. It is difficult to evaluate quantitatively the effectiveness of the antihistaminic substance, but the intensity of the allergic reaction in the treated animals was conservatively estimated and found to be at least 20 to 50 per cent lessened when compared with the control group (Table IIIA).

*Local Applications.* A second series of twenty guinea pigs was sensitized and then divided into two lots of ten animals each. The first lot, serving as controls, was challenged twice at twenty-four hour intervals, with 10 per cent p-phenylenediamine in petrolatum twenty-one days after the be-



Fig. 2. Guinea pigs sensitized to p-phenylenediamine; influence of pyribenzamine upon the blackening of the skin.

(Above) Challenged with the same ointment, but simultaneously treated with 5 per cent pyribenzamine oil in sesame oil.  
(Below) Challenged with 10 per cent p-phenylenediamine ointment.

ginning of the sensitization. The two challenging retests of the second lot were made with a 10 per cent p-phenylenediamine in petrolatum containing 2 per cent of pyribenzamine base. Simultaneously and during the next two days, both groups of animals received the following additional treatment: The control animals were locally treated twice a day with 0.5 ml. of pure sesame oil, the "pyribenzamine animals" with 0.5 ml. of a 5 per cent pyribenzamine base in sesame oil. As seen in Table IIIB, the results of this series were more pronounced than those of the preceding series in which pyribenzamine was injected. The control animals reacted with an unusually strong dermatitis and pronounced blackening of the skin, whereas all reactions in the animals treated with pyribenzamine were considerably weaker. The histological picture of the two reactions showed a severe dermatitis in the control animals, and an almost normal skin in the treated guinea pigs (Figs. 2, 3 and 4).

Results similar to those obtained with pyribenzamine were observed with 2339 RP (antergan) in a series of seventeen other animals strongly sensitized to p-phenylenediamine. Eight animals, serving as controls, reacted upon challenging with a four-plus reaction. The nine remaining animals were treated with 20 mg. per kg. body weight of 2339 RP,

## ANTIHISTAMINIC SUBSTANCES—MAYER

three times daily for two consecutive days. Only one of these animals showed the same strong reaction as the controls, while all the other animals reacted to a much lesser degree.



Fig. 3. (*Above*) Guinea pigs sensitized to p-phenylenediamine. Challenged and simultaneously locally treated as in Fig. 2. Skin almost normal—thin and tender.

Fig. 4. (*Below*) Guinea pigs sensitized to p-phenylenediamine. Challenged. Control: Strong inflammation of the skin with crust formation, scaling and thickening.

These experiments prove that antihistaminic substances are not only capable of suppressing or attenuating anaphylaxis and vascular sensitizations, but also sensitizations of the contact dermatitis type. However, another possible explanation had to be ruled out before one could assume that the activity of pyribenzamine in case of epidermal sensitizations is due to the neutralization of histamine and therefore due to the same mechanism which has been discussed in the two preceding series of sensitizations.

P-phenylenediamine is, as we already have discussed, an unstable substance, since living cells, such as the bacteria or the cells of the skin, the muscles, the liver, et cetera, oxidize it rapidly into the extremely

reactive quinone-di-imine. It has been shown in previous studies (Mayer<sup>13</sup>) that this oxidation product is the sensitizing substance and not the unchanged diamine.

As in the case of p-phenylenediamine, many other aromatic amines of various chemical structures are oxidized by the animal cells into quinone-H-imines or quinone-di-imines, and a number of these reaction products combine with the protein constituents of the cells. Only those which are able to combine with protein are strong sensitizing substances. The antigenic nature of an aromatic amine depends therefore upon certain well-defined chemical configurations.

These same oxidation products also play a role in sensitizations to various azo-dyestuffs. Earlier experiments which have been confirmed and extended by Stevenson, Dobriner and Rhoads<sup>20</sup> have shown that the living cell reduces certain azo compounds, for instance butter-yellow, splitting them into two aromatic amines. These amines are then oxidized as stated above.

There is much evidence for the supposition that these oxidation products are not only directly responsible for the allergic processes, but also for the proliferation of epithelial cells and for the cases of so-called "aniline-cancer" produced by intimate and prolonged contact of the epidermis and especially the mucosa of the bladder with azo compounds and aromatic amines (Mayer<sup>14</sup>).

The prophylactic activity of pyribenzamine in p-phenylenediamine dermatitis could be explained by an interference with the oxidation of p-phenylenediamine to the directly active substance, or with the combination of this oxidation product with certain cell components. In order to rule out this possibility, a series of experiments was undertaken in which the influence of pyribenzamine upon the production of atypical proliferation of the epithelium by certain aromatic amines was studied.

Atypical proliferations of the epithelium were produced by the injection of 1 per cent oily solution of p-phenylenediamine,  $\alpha$ -naphthylamine and butter-yellow on the inner surface of the rabbit ear. On other corresponding sites these same substances were injected together with a 1 per cent solution of pyribenzamine base in sesame oil. The injections were repeated twice weekly for four weeks, at the end of which time the resulting lesions were examined histologically. No differences were observed in the intensity of epithelial proliferations, regardless of whether pyribenzamine was administered.

These experiments have shown that pyribenzamine does not interfere with these typical, but non-inflammatory and non-allergic activities of p-phenylenediamine and other aromatic amines. The negative results are another proof for the specific, anti-allergic action of pyribenzamine.

*B. Sensitizations to 2, 4-dinitrochlorobenzene.* Sixteen guinea pigs were sensitized to dinitrochlorobenzene according to the method of Land-

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TABLE IV. INFLUENCE OF 10 MG./KG. BODY WEIGHT OF PYRIBENZAMINE UPON THE DERMATITIS PRODUCED WITH DINITROCHLOROBENZENE IN SENSITIZED GUINEA PIGS

Number of Animals	Degree of Sensitization	Pyribenzamine Administered	Reaction			
			+++	++	+	0
6	Strong	None	6	0	0	0
6	Strong	10 mg./kg.	1	1	4	0
2	Controls, no sensitization	None	0	0	0	2

steiner and Chase.<sup>7</sup> Ten of the sixteen animals received a subcutaneous injection of 10 mg. per kg. body weight of pyribenzamine, fifteen minutes before the challenge with 1 per cent dinitrochlorobenzene in oil, and five similar injections during the following forty-eight hours.

The results were similar to those obtained in the p-phenylenediamine sensitizations. All six unprotected and sensitized animals showed, upon challenge with the antigen, extensive inflammation, and only one of the ten animals treated with pyribenzamine gave a similar strong reaction. The inflammation produced in the nine other animals treated with pyribenzamine was much weaker. A cross experiment was performed ten days later. Animals which had previously served as controls were then treated with 10 mg. per kg. body weight of pyribenzamine, while the animals which were previously treated with this antihistaminic substance, served now as controls. The results obtained corresponded closely to those of the first phase of the experiment: the unprotected animals again showed a severe dermatitis, in contrast to the pyribenzamine animals which had significantly much slighter degrees of inflammations (Table IV).

It is concluded from the various experiments that pyribenzamine has a definite effect upon experimental contact dermatitis. However, this effect is much weaker than in the case of anaphylaxis or vascular sensitization. The best results were obtained when the antihistaminic substance was locally applied.

## DISCUSSION

The results of the present study of the influence of pyribenzamine upon three different types of sensitizations are as follows:

Anaphylaxis and that condition closely related to it, namely, sensitization of the vascular apparatus of the guinea pig skin, respond easily to treatment with an antihistaminic substance. It is possible to prevent completely or suppress all manifestations with moderate and nontoxic doses of pyribenzamine.

In contrast to these two forms of experimental allergies, sensitizations of the contact dermatitis type are much more resistant to treatment with

pyribenzamine, although in almost all cases the antihistaminic compound had a definite beneficial influence.

In anaphylaxis in guinea pigs, pyribenzamine in doses of 0.5 mg. to 1 mg. per kg. body weight was capable of conferring effective protection to more than 50 per cent of sensitized animals, and slightly higher doses protected all treated animals.

In the case of the vascular sensitization of guinea pigs, 10 to 25 mg. of pyribenzamine per kilogram body weight were required.

Whereas in anaphylaxis or vascular sensitization mentioned above, all symptoms were prevented or completely disappeared with the antihistaminic treatment, the epidermal sensitization of the contact dermatitis type responded only partially to treatment with the highest doses of pyribenzamine which could be used safely. In many animals, ameliorations approaching 50 per cent were obtained, but in no animal was there complete protection.

The various types of sensitization showed not only considerable differences in the response to the treatment of the allergic manifestations with pyribenzamine, but there were also great differences when pyribenzamine was administered prophylactically to prevent the outbreak of the various types of allergic manifestations.

Differences in the therapeutic activity of pyribenzamine can be anticipated because it is to be expected that a dermatitis would regress more slowly than a wheal under similar treatment, since considerably more tissue repair is necessary, but the differences in the response to prophylactic treatment must be due to other reasons. We believe that a close relationship exists between the effectiveness of an antihistaminic substance in a given allergic process and the sensitivity of the particular cell system toward histamine, which is the site of the given sensitization. In other words, it is supposed that a certain form of allergy is highly responsive to the anti-allergic treatment because the cell system at the site of this specific allergy or the animal species in question are highly sensitive to histaminé, and vice versa.

Such functional differences have indeed been observed in the various types of sensitizations dealt with in these present experiments. The chief anaphylactic shock tissue of the guinea pig, namely, the smooth muscle, is extremely sensitive to histamine; accordingly, guinea pig anaphylaxis is highly responsive to antihistaminic treatment. The vascular apparatus of the guinea pig skin is less sensitive to histamine than smooth muscle, and considerably more pyribenzamine is required to influence the allergic manifestations localized in the vascular system of the skin. The cells of the guinea pig epidermis do not respond to a single, short poisoning with histamine as do the smooth muscles or the capillaries. Consequently, the epidermal sensitization responds to pyribenzamine only when very high doses are administered. The fact, however, that they did respond seems to prove that the epidermal cells are, to a certain extent, sensitive



to histamine and it would certainly be interesting to investigate the influence of a prolonged local histamine poisoning upon the epidermis.

We observe the same relationship between histamine sensitivity and the response to antihistaminic treatment not only in various organ systems of the same animal, but between animal species as well; the following example is illustrative:

It is known that the mouse is about 1,000 times more resistant to histamine than the guinea pig; likewise, it is generally known that mice can be sensitized to proteins only with extreme difficulty. Mice become anaphylactic when sensitized with doses of serum or egg white which are more than fifty times greater than those required in anaphylaxis of guinea pigs.

Mayer and Brousseau<sup>16</sup> have studied the influence of various antihistaminic substances upon mouse anaphylaxis. It was found that pyribenzamine, for instance, was more than fifty times weaker in activity in mouse anaphylaxis as compared with the activity in guinea pig anaphylaxis. Of the control mice 89 per cent died of anaphylactic shock, while only 42 per cent succumbed after a prophylactic injection of 25 mg. per kg. of body weight of pyribenzamine. Thus, in mouse anaphylaxis, pyribenzamine is no more active than in contact dermatitis of guinea pigs.

Apparently a general and common law exists which regulates the relationship between sensitivity to histamine, facility to sensitize, and response to antihistaminic substances. Up until now, only the first part of this law, namely the relationship between histamine sensitivity and allergic sensitization, has been discussed. The inclusion of the effectiveness of antihistaminic therapy is certainly important, especially if we study the mechanism of action of the various factors involved.

The mechanism through which antihistaminic substances prevent anaphylactic shock or alleviate other allergic manifestations is still unknown. Most investigators believe that these substances compete with histamine or histamine-like substances in certain enzyme systems. In our opinion, this "competitive theory" is strongly supported by the fact that relations exist between the sensitivity to histamine and the response to anti-allergic treatment with antihistaminic substances.

At first, the consistently fair results obtained with pyribenzamine in experimental contact dermatitis were somewhat surprising to us, since we were used to almost completely negative results in dermatitis in man. It is possible that these differences between man and experimental animals are mainly due to differences in dosages of pyribenzamine which were in all instances much higher in guinea pigs than in man. It might be necessary to obtain a minimum level of antihistaminic substance at the site of the pathological process, as suggested by the fact that the best results were obtained when pyribenzamine was locally applied.

There is, however, another possible explanation for the increased effectiveness of locally applied pyribenzamine. Pyribenzamine, like all

known antihistaminic substances, has a relatively strong local anesthetic activity. Anesthetics can prevent the development of primary and allergic skin irritations, and it might well be possible that the pyribenzamine ointment prevented the outbreak of the p-phenylenediamine dermatitis in this way. However, it is hard to believe that such an explanation also holds for the definite activity which pyribenzamine displayed when injected subcutaneously, since anesthetics are active by parenteral application only when injected into or beneath the diseased tissues.

If the result observed in this study should be confirmed by further experiments, the fact that antihistaminic substances are effective not only in allergies of the anaphylactic type, but also in contact dermatitis—at least to a certain extent—may bridge the gap which still exists between the various members of the allergy family and may bring contact dermatitis closer to the other forms of allergy. The results obtained in this study would indicate that the common denominator in all skin allergies studied here is histamine or a histamine-like substance.

#### SUMMARY

Antihistaminic substances, which are a very important addition to the therapy of allergic diseases, also constitute a very useful tool for the study of allergic conditions. Its use enables us to detect the activity of histamine or a histamine-like substance and its role in various allergic diseases. During the present investigation it has been shown, with the help of this tool, that histamine or a histamine-like substance is not only an important factor in anaphylaxis and allergic manifestations which are closely related to anaphylaxis, but also in certain other manifestations which until now have not been associated with histamine. Indeed, pyribenzamine, a substance exhibiting strong and specific antihistaminic properties, exerts a definite activity in experimental dermatitis. This fact suggests that an H substance also plays an important role in contact dermatitis, thus connecting this disease to anaphylaxis and other allergies of an anaphylactic nature.

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# DOES THE ROUTINE TREATMENT OF ASTHMA NEED REVISION?

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A DISCUSSION on treatment of a disease must necessarily be biased by one's own experience. In asthma, a disease which is subject to spontaneous remissions and to psychogenic improvements, the patient's personal interpretation of results further confuses the issue. Although we may have employed certain therapeutic procedures for many years, we are just becoming aware of certain shortcomings in them. These shortcomings are the subject of this paper.

There are two objectives in treating asthma: first, to remedy the constitutional deficiency; in other words, to restore the patient to the same state as that of his brother or sister who have also inherited the allergic constitution but have never developed asthma; second, to make him comfortable, i.e., to afford him symptomatic relief.

## CAUSATIVE TREATMENT

The methods available to us for improving the constitutional weakness are elimination, hyposensitization and counteracting infection.

## ELIMINATION

Concerning food elimination, we have in the past established certain undesirable habits. They arose from the fact that in a small percentage of asthmatics, a history of sensitization to some food is easily obtained and, indeed, an actual cure may be effected by its elimination. Such cures are very dramatic and relatively easy to accomplish. They, therefore, led, in the early period of the development of our knowledge, to the belief that food is the most important offender in asthma. Accordingly, extensive dieting has been and still is being practiced. Some patients observe these diets for years. Indeed, some allergists, themselves afflicted with the disease, have been avoiding certain foods for years, insisting that this is essential for their well-being. Lay persons and doctors alike have preached the gospel of food sensitization for years. It appeals to people. Some patients have thus been led since early childhood to become neurotics. They go through life fanatically adhering to their diets. What are the facts?

As early as 1924, Duke<sup>1</sup> recognized ragweed pollen as the "most important single cause of chronic asthma." In 1933, I demonstrated that most perennial asthma originates from pollen, especially from ragweed.<sup>7</sup> I then observed a fact recently re-emphasized by Tuft<sup>5</sup> that most chronic asthma originates at the termination of the ragweed season. This type of asthma can be promptly aborted by a few injections of ragweed extract even at a time when ragweed is no longer in the air, no dieting being re-

<sup>1</sup>Read at the meeting of the American College of Allergists, San Francisco, California, June, 1946.

quired. A similar peak of asthma at the termination of the tree season and a less pronounced one at the end of the grass season contribute to the chronicity of asthma in summer, sensitization to house dust, to cold temperature and infections in winter. This predominance of climatic factors

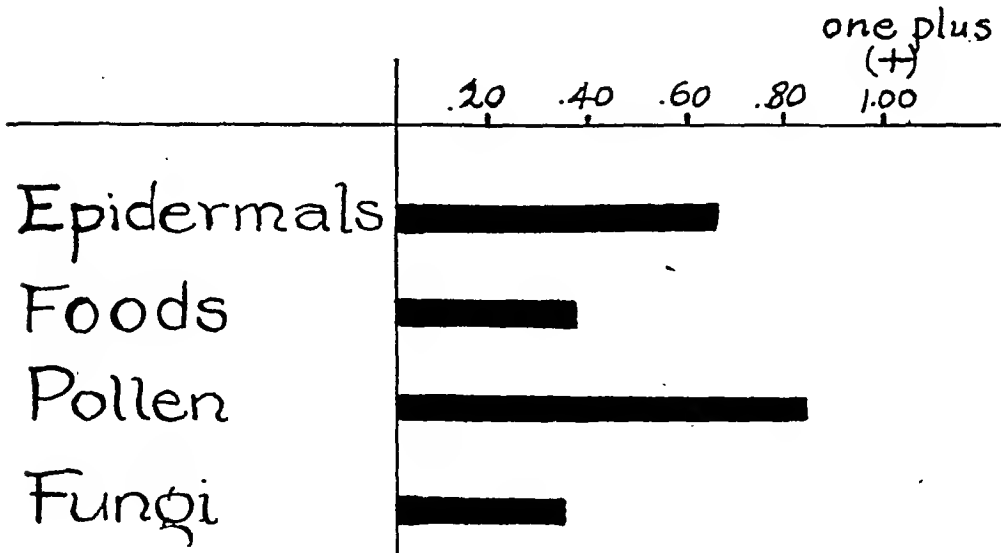


Fig. 1. Graphic representation of the average positive intradermal skin reactions for each group of antigens on 439 patients with chronic asthma.

in contrast to food is further indicated by the following: Most asthmatics present themselves at the office on the same days. Skin reactions to pollen are by far the most constant ones and do not tend to disappear on second and third testing as do reactions to foods; patients who are sensitive to foods are clinically most reactive to these foods at the time of pollination. Pollens produce the strongest skin reactions, as indicated in Figure 1. This is followed by epidermals, while fungi and food react much less. In certain individuals, it is true, such substances as animal hair, upholstered furniture, dust from a bakery in the neighborhood, or foods are the dominant causes of chronic attacks, but such instances are by far in the minority.

Accordingly, I am guided by the following rules:

1. Food is eliminated only if the patient volunteers the history that it is responsible for attacks; if the skin tests reveal a few outstanding reactions in a patient whose tests are otherwise inconclusive; if other means of relief have failed.
2. Elimination of food is carried out at the most only for two weeks, whereupon gradually increasing amounts of this food are systematically introduced.
3. In young children in whom food is more significant than in adults, hyposensitization for such items as egg, milk and wheat may be occasionally considered if they are clinically dominant.

I have recently experimented on emaciated asthmatics with high caloric diets, disregarding their food sensitivity altogether. This has been surprisingly successful.

We are in the habit of eliminating many articles other than food. Regarding house dust, for instance, very elaborate directions have been prepared for physicians—incidentally, mostly by lay persons. Indeed, some patients judge the ability of an allergist by the number of pamphlets handed to them imposing restrictions. Are such procedures reasonable? Assuming that a room can actually be made free from dust and that all the rugs and upholstered furniture can be eliminated from a home, is it not likely that the patient will be less resistant to house dust when he enters another home which is not dust free, as he must do sooner or later? Furthermore, I am not impressed with the curative effect of air filtration in asthma. Whereas, some patients report temporary improvement thereby, sudden changes in air content and temperature on leaving the room often elicit severe attacks. A well-known air filter corporation has recently placed filters in the homes of eighteen of my patients, encouraged by the report of a well-known allergist who experienced remarkable results. Although both dust and pollen filtration were very effective, the improvement of the patient was negligible.

In animals, anaphylaxis is induced by an injection of an antigen two to three weeks following a preliminary sensitizing dose, while frequent injections administered during the three weeks' interval protect the animal from shock. Ingestion and inhalation of the antigen elicit shock in the same manner as demonstrated by Ratner.<sup>4</sup> Similarly, my own observations have convinced me that asthmatics absorbing an antigen repeatedly at short intervals suffer less than if this antigen is avoided strictly and then happens to be accidentally inhaled or ingested. Those who visit a horse stable or play in a hay stack once or twice a year develop much more asthma than those doing this habitually. The cashew nut or the lobster eaten two or three times a year is much more harmful than if eaten daily. The same holds true with inhalation of house dust.

There is another much more serious aspect to this question: We find that many of our patients are neurotics. By imposing too many "don'ts" on them and by trying to place them literally in a glass house, we succeed in isolating them psychologically from their surroundings at the very beginning of their lives, and provoke most serious inferiority complexes. We refer them to psychiatrists for psychoanalysis, realizing that their disease is aggravated by psychogenic factors, but we fail to see that we ourselves are chiefly responsible for it.

What solution can be offered instead? There can be no objection to advocating cleanliness in a home, nor to using a rubber cover on the mattress and on the feather pillows. In certain cases, the elimination of a dog or a cat or even the temporary removal of the patient from his home is indicated. However, I no longer prescribe avoidance of all animals, nor prohibit riding through the countryside, playing out of doors, or picnick-

ing. Instead, the patient is merely warned to be on guard lest such exposures produce symptoms. In fact, the patient is encouraged to live a normal life as much as possible.

Since physical exercise, sometimes even the slightest exertion, aggravates asthma, an attempt is made to establish a threshold in the patient's tolerance to effort. He begins with very light exercise such as walking, climbing stairs, bending, squatting, two to three times a day; at first with moderation and indeed with caution. This program is initiated as soon as an attack has subsided. It is intensified at the time when the patient is completely free from attacks. If the improvement continues, activities such as playing golf, bicycle riding, climbing, hiking and even swimming, playing football and baseball and horseback riding are encouraged. If not tolerated, it is discontinued for a few days or weeks. The boost of the patient's mental attitude by letting him perform these normal activities which had heretofore been forbidden, almost universally outweighs any temporary ill effect.

This principle of gradually building up a tolerance is further utilized in another manner: Practically all asthmatics are "sensitive" to sudden temperature changes; some develop severe attacks when exposed to cold temperature. Duke's<sup>2</sup> proposal to build up a resistance to cold has been a distinct adjunct to our treatment. It consists of gradually exposing the skin to cold water through sponging arms and legs at first, and later rubbing ice on the body surface. Some patients thus acquire the habit of taking a cold bath daily.

It is not necessary to dwell at length on the advantages and disadvantages of a change of climate. To the physician, this measure serves too often as a means of ridding himself of a patient upon whom his treatment has otherwise not been successful. The patient, on the other hand, considers the breaking up of his home and moving to a different climate as his last resort. If this experiment fails, despondency and despair ensue. To recommend a change of climate is, therefore, a grave responsibility. A thorough investigation should be made of the prospective climate with regard to content of pollen and fungi and this should be thoroughly checked against the clinical background of the individual. It is particularly harmful to send the patient into a pollen-free area and have him return at the height of a pollen season. Thus hay fever sufferers frequently develop their first asthma because they return at the termination of the school vacation which coincides with the peak of the ragweed season.

#### HYPOSENSITIZATION

Hyposensitization in asthma is necessarily inferior to the ideal type of desensitization in animals. For, in asthma, there is practically always a multiplicity of antigens, there is a more prolonged and continuous absorption of the antigens through ingestion and inhalation, and secondary infection is apt to complicate the clinical picture. An approach to the ideal

desensitization can be attained if we select correctly the dominant antigen and administer the right dose at the right time.

In my own work the following practices are stressed which deviate somewhat from the usual textbook method:

1. In chronic cases of asthma, all pollen and fungi which are major causes in this area, are administered throughout the year in such a manner that the highest dose is reached shortly before the respective season. In winter, house dust and bacterial antigens are added, as well as any other inhalants indicated by the patient's clinical behavior.

2. During acute attacks, instead of the usual treatment, very small doses of the above antigens are given at intervals of two to four hours. These doses are not increased.

3. Shortly before, or at the beginning of a pollen season, short interval hyposensitization with increasing doses, described by myself and Ascher<sup>8</sup> and recently stressed by Loveless,<sup>3</sup> is especially helpful. In any type of desensitization, we guard carefully against overdoses which constitute the most common reasons for its failure.

#### COUNTERACTING INFECTION

Considerable confusion exists concerning the role played by infection in lowering the threshold of the allergic constitution. In the past we have learned to condemn such procedures as tonsillectomies, submucous resection, polypectomy, and sinus operations because they not only failed to cure asthma but sometimes aggravated it. It would be equally wrong to be dogmatic and to disregard these procedures entirely. When true infectious processes in tonsils, nose and sinuses are clearly differentiated from allergic irritations not on the basis of nasal smears and similar laboratory procedures, but on critically sizing up the whole clinical picture, those surgical procedures are effective. Even vaccine injections, which so often aggravate asthma, are indicated in selected cases, provided the doses are very cautiously gauged. In a small number of asthmatics who exhibited strongly positive tuberculin reactions, I have even employed, with striking success, highly diluted tuberculin injections.

The advent of sulfa drugs and penicillin constitutes a definite boost in the treatment of the chronic asthmatic, in spite of the fact that occasionally sensitization from these drugs occurs. The presence of purulent sputum and nasal secretions, fever, and leukocytosis form the chief indications for this treatment. Acute intercurrent infections in chronic asthmatics are effectively combated by penicillin and sulfa. I prefer the introduction of large doses of penicillin with beeswax, or repeated small doses of penicillin, to the inhalation method.

#### SYMPTOMATIC TREATMENT

The principal objective in symptomatic treatment is elimination of mucus from the bronchi and relief of bronchospasm. Here, too, we have acquired

undesirable habits. Most of us recognize the need for extreme caution in administering such drugs as morphine and aspirin. It is less appreciated that some of our standard medications in asthma which are believed to be indispensable are not only not necessary, but actually harmful. Once the patient is given a hypodermic syringe or an atomizer and epinephrine, he will reach for it at the slightest provocation. He feels that he is more up to date if he uses epinephrine in oil instead of the aqueous solution. On many occasions, I observed through substituting saline placebos for epinephrine, that the relief derived from the drug is largely psychological. Doses not larger than 1/20 c.c. or 1/10 c.c. are sufficient in most attacks. If such doses are not effective, larger ones will be equally useless. Epinephrine in oil and the epinephrine spray are undesirable because it is impossible to control the absorption satisfactorily. I do not *routinely* prescribe ephedrine and ephedrinelike drugs every three or four hours, since I have observed patients in whom the elimination of such routine medication resulted in complete cessation of attacks.

It is surprising that by far the best treatment for asthma, first suggested by me in 1938,<sup>6</sup> has not been generally adopted. The mechanism of an attack and the usual mode of death is obstruction of bronchi with mucus and subsequent atelectasis of pulmonary areas. Therefore, it is logical to assume that the elimination of mucus from the bronchi through bronchoscopic aspiration followed by a lavage of the bronchial tree with saline solution will relieve the most severe or chronic attack. In a large percentage of my patients it has been a life-saving procedure. When it was first employed, occasionally serious difficulties were encountered, not from the treatment itself, but from the use of local and general anesthetics and from other medications given either before or after. Since we have eliminated anesthetics and drugs completely with the exception of barbiturates before the bronchoscopy, we have had no ill effects. The treatment is now an office procedure. It has proved by far the most valuable measure in the treatment of asthma.

#### SUMMARY

In the customary treatment of bronchial asthma, attention is being directed towards the control of individual attacks with little emphasis on the rehabilitation of the patient's health after the attack has subsided. Whereas, it is necessary, during an attack to eliminate foods, airborne antigens, and to restrict physical activities, harm can be done by undue extension of such measures after the subsidence of the attack. Such practices not only retard the patient's recovery, but constitute the main factor in causing a psychosomatic aggravation of the disease.

In view of this fact, a program is outlined which is designed to overcome chronic invalidism of the asthmatic. It consists of cautious institution of carefully gauged light exercise; gradual exposure to such antigens as animal emanations, house dust, et cetera; institution of high caloric

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## ECZEMATOID MONILID OF THE EYELIDS ("CANDIDID")

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THE eczematous syndrome which is the subject of this paper is a "monilid" or rather a "Candidid"; that is, a cutaneous allergic manifestation caused by *Candida albicans*. This condition is characterized by the following triad:

1. It occurs with preference in the female sex.
2. It is localized on the eyelids and is always bilateral.
3. It usually appears in spring and fall.

We have observed this clinical entity for over three years.\* I am presenting the results obtained so far as a preliminary note, so that others interested in this subject may repeat the experiments and confirm my findings.

We are dealing with an eczematous cutaneous syndrome which affects preferably women, without distinction of age or social status. It is localized on the upper and lower eyelids of both sides and it is almost always accompanied by an eruption of the lips and neck (neurodermatitis of the dermatologist); the latter is usually bilateral, although not always. It is a dry, scaly and severely itching dermatitis, which appears spontaneously in spring and usually disappears just as spontaneously during summer, only to reappear in the fall and heal again in winter. It is not always a seasonal affair. Some patients do not exhibit such a fixed cycle; others are affected continuously during two or more consecutive seasons. Some cases seem to have only seasonal remissions or aggravations, while the disease itself continues throughout the whole year.

Intradermal tests were performed with an active extract of *Candida albicans*, made according to the specific technique of P. Negroni. Our patients showed both immediate and delayed reactions. Reagins could not be demonstrated. In those cases where passive transfer was attempted, we obtained negative results. In two patients, only delayed reactions could be elicited. In all these experiments, controls were performed with injections of the culture medium. Thus, the possibility of "immediate" reactions due to the action of peptonés was confirmed.

The treatment of this type of eczema consisted of subcutaneous injections of an aqueous extract of *Candida albicans*. It was successful in the great majority of cases; the results varied between a total cure and some degree of improvement, which was never less than 50 per cent. No other treatment produced better results. In some cases, the pruritis disappeared after the first injection and the cure was completed after a few days of treatment. In some exceptional cases we were not able to cure our patients.

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\*We shall continue these studies; they will be the subject of a more comprehensive paper which will be published later in collaboration with my co-workers, Dr. Miguel Agustín Solari and Dr. Alois E. Bachmann.

I believe that the syndrome described is an allergic manifestation due to sensitization from *Candida albicans*. There is proof that we are dealing with a "specific," "acquired" and "altered" reaction to this antigen.



Figs. 1 and 2. Characteristic eczematous lesions involving the periorbital region.

The following evidence is presented to demonstrate that this type of dermatitis is a special and frequent manifestation of a monilid ("Candidid").

1. Absence of mycotic infection at the site of the affection.
2. Existence of an "infectious" or "tuberculin-type" allergy, as evidenced by the positive delayed reactions to the extract of *Candida albicans*. *Candida albicans* was indicated as the specific causative allergen by the positive skin tests.
3. Exacerbation produced by injection of an excessive quantity of the extract of *Candida albicans*.
4. Complete cure following treatment with an extract of *Candida albicans*, at a time of intense discomfort, when the assumption of a spontaneous regression was impossible. The rapidity of the cure is another factor which authorizes us to assume a real and effective therapeutic action.
5. The existence of an intestinal focus of *Candida albicans*, manifested either as a mycotic infection or as the presence of colonies of that fungus in the intestinal tract. Sometimes there was also an interdigital cutaneous focus of the feet.

Negroni has shown, what hitherto had not been realized, that this fungus is found very frequently in the human intestines. It cannot be diagnosed clinically because this infestation does not produce typical manifestations. Any focus or "parasitization" by *Candida albicans* may produce the syndrome of an allergic "Candidid" of the eyelids. Theoretically, the location of the mycotic focus is of no importance, the presence of an active, allergizing, exo-palpebral focus being enough. Therefore, the requirements are meant to include the syndrome described among the tissue reactions of allergic origin.



Fig. 3. Characteristic lesions of the lips usually accompanying the eruption.



Fig. 4. The eczematous cutaneous syndrome as it involves eye, lips, face and neck.

The existence of a family history of allergy in some of our patients and the bilateral localization of the syndrome make us think of the possible action of an hereditary factor which at the moment cannot be considered



Fig. 5. "Candidid"—characteristic eruption of the neck.

as of the atopic type, as it was not possible to prove the existence of reagins. We know that reagins are not a pathognomic sign of atopy, but we also know that they always exist in atopy. In this form of allergy the symptoms are always bilateral and the same occurs in the syndrome "Candidid."

Until an international agreement is adopted, we believe that, according to our classification, the "Candidid" I am describing can be included provisionally in the "nonreaginic allergies." Further studies will show whether it corresponds to the familial or to the nonfamilial form.† There are a number of other interesting observations which we shall continue to study.

In cases of phlyctenular conjunctivitis, characteristics similar to those of "Candidid" are present: presence (not always) of an allergic family history, delayed positive skin reactions to tuberculin, rapid cure from injections of tuberculin, and bilateral occurrence. It should be understood that I refer only to cases of allergic phlyctenular conjunctivitis in which the causal allergen is the bacillus Koch. I am certain about these facts, as I have cured a sufficient number of patients of this type.

The success we had with the treatment based on injections of an extract of *Candida albicans* reminds us of observations made during co-seasonal

†This classification was presented at the Pan-American Congress of Allergy in San Francisco, June, 1946.

treatment of pollinosis. For unknown reasons, it is possible to obtain a cure in spite of the continued activity of the causal allergen. (The same occurs in the cases of phlyctenular conjunctivitis during tuberculin treatment.) In some patients, the curative dose is very close to the reaction producing dose. Three Coca units cured, while four units provoked the

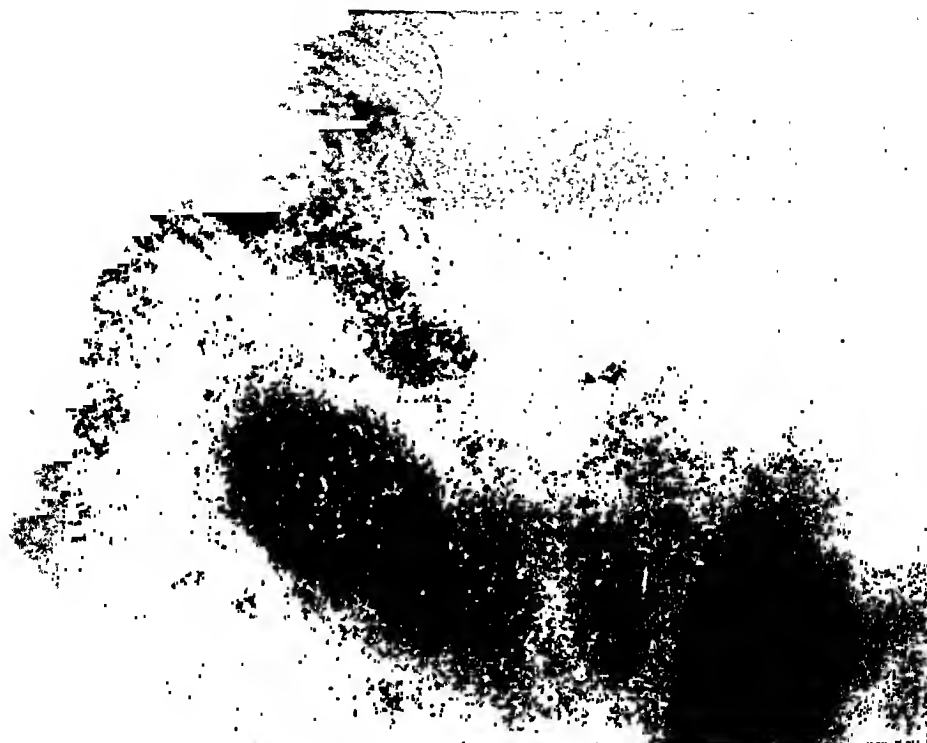


Fig. 6. Enlargement of Figure 5.

syndrome. In other cases, it was necessary to inject up to 1,000 Coca for a therapeutic effect. The dosage must be adapted to every patient; it is not possible to give a general scheme.

The following observation is noteworthy. In one patient who suffered from this symptom for several years, one additional dose of the antigen, beyond the tolerated dose, produced a recurrence during the season when the patient normally was free from the dermatitis.

In the few instances in which we could not obtain a cure, we think that this occurred because the quantity of active endo-allergen made impossible the reaction of "hypertolerance" which we sought. This fact seemed to us similar to what occurs in cases of "bacterial allergic asthma by bronchial infection" when attempting, without success, hyposensitization during the period of full activity of specific bronchial infection.

In conclusion, we have found that, for unknown reasons, in many women, the existence of *Candida albicans* in the intestines or in the skin provokes an allergic condition and allergic skin manifestations. These are frequently seasonal, localized preferably on the eyelids, the lips and the neck, characterized by a dry, very pruritic eczema which we may consider at present as a form of allergy "of infection," tuberculin-type.

## TIMOTHY VERSUS BERMUDA GRASS

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THE important question of the antigenic similarity or dissimilarity of the various hay fever grasses has long been, and still remains, controversial. The early studies of Sheppegrell and others pointed out that there was close similarity of antigen throughout all the grasses. However, Watson and Kibler (1922) in Tucson, Arizona, were quite emphatic in denying this to be the case with timothy and Bermuda grass; they say, "The larger number of our cases who showed a reaction to Bermuda grass were absolutely negative to timothy." Similarly Phillips (1928), reporting from Phoenix, Arizona, states that, as a result of cross sensitization, eastern ragweed cases usually have hay fever the first year of their arrival in Arizona. Such, however, is not true of the eastern grass cases; in Arizona they are nearly always free from hay fever for three to five years before they succumb to the effects of Bermuda grass pollen.

It is important to note that both of these reports come from regions in which Bermuda is almost the sole cause of grass hay fever, and timothy and the four other major causes of grass hay fever in the East are entirely absent.

Valuable as these observational data are, they lack the authenticity of the controlled experiment. Such experiment appeared to have been furnished by Chobot (1929). He observed that ten eastern hay-fever cases, who had never been exposed to Bermuda grass pollen, when tested (ophthalmic and intradermal) with timothy and Bermuda, showed reactions equal in all. He then put this to the test by the method of cross desensitization of passively sensitized skin sites. He sensitized the sites by means of the serum of one of these cases. When these sites were completely desensitized by daily injections of Bermuda they proved to be negative to timothy. Or conversely, when desensitized to timothy, they became negative to Bermuda. This is *prima facie* evidence that the two pollens he was working with were identical.

Similarly, Stull, Cooke and Barnard (1932), using the *in vitro* neutralization method, reported that the active substances of timothy and Bermuda pollen were identical.

Results in conflict with these were obtained by Piness and Miller (1930), reporting from Los Angeles, California, a Bermuda grass region. These investigators found in their clinic that they obtained single reactions to ten different grasses, Bermuda topping the list with forty-five cases out of four hundred and fifteen. By means of cross desensitization they found that with some sera Bermuda desensitized for timothy, but with others only for Bermuda. And with some sera timothy desensitized for

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Read at the meeting of the American College of Allergists, San Francisco, California, June 28 to 30, 1946.

## TIMOTHY VERSUS BERMUDA GRASS—WODEHOUSE

TABLE I. TIMOTHY AND BERMUDA COMPARED WITH JB AND BR SERA.  
REACTIONS OF SENSITIZED SITES.

Clix	JB Serum						BR Serum						
Serum	Timothy 500 u			Bermuda 500 u			Serum	Timothy 500 u			Bermuda 500 u		
dil. <sup>n</sup>	W	E	(E-W)W	W	E	(E-W)W	dil. <sup>n</sup>	W	E	(E-W)W	W	E	(E-W)W
1:20	14	55	574	12	45	396	1:10	9	11	18	10	40	300
1:20	13	50	481	10	40	300	1:10	8	30	176	11	50	429
1:100	15	60	675	10	30	200	1:1	10	50	400	11	80	759
1:100	13	50	481	10	30	200	1:10	Timothy 270 u			Bermuda 270 u		
1:100	13	50	481	10	25	150		7	15	56	7	40	231
1:100	14	60	614	9	35	231							

W—wheal, E—erythema dia. in mm. (E-W)W—reaction intensity.  
Sensitization 0.05 c.c. Test 0.01 c.c. intradermal

Bermuda, but in most only for timothy. From their results these authors conclude that Bermuda grass is much more nearly the perfect desensitizer than timothy:

At any rate, the available evidence in the controversy leaves an impression that the atopens of timothy and Bermuda are not identical, nor is the behavior of all grass-sensitive sera toward these two grasses identical.

In order to obtain information on the relationship between the atopens of timothy and Bermuda grass pollen, two sera were secured from grass-hay-fever cases. One (JB) was from a "Class A" case, a man of cosmopolitan habits. He had lived in the eastern United States where timothy is one of the commonest grass pollens. He had also lived in the western United States where Bermuda grass pollen predominates, and in various European countries where other grasses predominate. And everywhere he reported suffering from grass-hay fever. The other serum (BR) was from a "Class B or C" grass case, one who had developed hay fever in southern California, probably almost exclusively through exposure to the pollen of Bermuda grass.\*

Using these sera in passive cutaneous sensitization, we found that JB serum in a dilution of 1:1,200 sensitized well to timothy at 100 N. units per c.c., and somewhat less to Bermuda at 1,500 units. It was found that BR serum could be used at a dilution of 1:80 for Bermuda but no weaker than 1:20 for timothy. Thus the BR serum is much weaker than the JB

\*We are indebted to the late Dr. R. W. Lamson of Los Angeles, California, and to patients in his private practice for the sera used in these experiments.

The Bermuda grass pollen was obtained from T. R. Stemen, pollen collector of Oklahoma City. It was the product of a high yielding strain of this species selected by the writer and Mr. Stemen and cultivated on the latter's pollen farm. The timothy pollen was obtained from Greer and Greer, pollen collectors of Princeton, West Virginia. Both pollens were proved microscopically to be free from contamination and true to their identification. In such studies as this it is essential that the pollens employed be of known origin and purity. The discrepancies between the results of previous investigations may have been due to lack of attention to this detail.

serum and it is impossible to adjust them to equality by dilution, to both antigens at the same time, because their responses to these vary inversely.

The different behavior of these two sera toward timothy and Bermuda is more clearly revealed in some tests in which the two pollen extracts

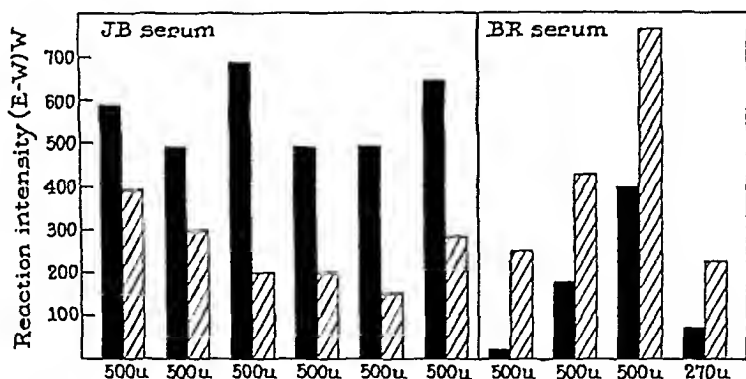


Fig. 1. Reaction intensities of timothy and Bermuda compared with JB serum (left) and BR serum (right). Solid shading indicates timothy; oblique lines indicate Bermuda.

were directly compared in opposite sites, with both JB and BR sera (Table I and Fig. 1). In six tests in which the two pollen extracts were tested against JB serum in equal N. concentration on corresponding sites, the timothy reactions were always very much larger than the Bermuda, indicating that the timothy extract is many times as effective as Bermuda. But when the same two extracts were tested against BR sites, the reverse was the case; the difference here was even more marked in favor of the Bermuda extract. Clearly, the difference between timothy and Bermuda is not merely quantitative. This opposite behavior of the two grasses in their reaction-provoking capacity towards two different sera also suggests the presence of two reagins, the serum of JB containing predominantly timothy reagin and that of BR predominantly Bermuda reagin.

This is further brought out when comparative neutralization experiments are done with the two pollens to discover their relative values in neutralizing each of the two sera. The first was done to find out the relative values of timothy and Bermuda in neutralizing JB serum (Table II). This is an *in vitro* neutralization test. Serial concentrations of Bermuda extract are combined with equal amounts of the serum, incubated and tested in normal sites on the right arm of a normal recipient. These are compared with symmetrically opposite tests made with timothy on the left arm. The first tests (right and left columns 1) are only of passing interest in that they show that the sensitizing serum and antigen introduced simultaneously elicit reactions, which the negative control shows are not serum irritation. The re-test with Bermuda at 5,000 units per c.c. (columns 2), on the right arm shows that a concentration of 4,434 units per c.c. of Bermuda was almost enough to desensitize a JB site. While the



## TIMOTHY VERSUS BERMUDA GRASS—WODEHOUSE

TABLE II. TIMOTHY VERSUS BERMUDA IN NEUTRALIZING JB SERUM. REACTIONS OF NORMAL SITES TO MIXTURES OF JB SERUM AND DILUTIONS OF TIMOTHY AND BERMUDA, AND HOMOLOGOUS AND RECIPROCAL RETESTS

Cxlix	Left Timothy						Right Bermuda						
Tim. Units	1. Test JB + Tim.		2. Retest Tim. 1,000 u		3. Reciproc. B'da 5,000 u		1. Test JB + B'da.		2. Retest B'da 5,000 u		3. Reciproc. Tim. 1,000 u		B'da Units
p. c.c.	W	E	W	E	W	E	W	E	W	E	W	E	p. c.c.
0.0	6	0	10	60	5	0	7	0	9	50	8	45	0.0
→88.2	8	40	→7	15	6	0							
154.4	7	35	5	12	5	0							
270.2	8	40	5	0	8	12							
472.8	7	40	5	0	9	15	8	35	9	40	10	50	472.8
827.4	7	35	5	0	8	15	8	30	7	25	8	45	827.4
							8	30	8	30	10	50	1448.
							8	20	8	30	11	40	2534.
							7	0	→7	20	10	35	4434.←

1. Test: 0.05 c.c. JB serum 1:20+ serial dilutions of timothy and of Bermuda *in vitro* one hour room temperature.

2. Retest: 0.01 c.c. Bermuda 5,000 units per c.c. and timothy 1,000 units per c.c.

3. Retest: reciprocal.

Dilution series 1.75X. Bermuda = 5.36X timothy.

timothy dilution series, on the left arm, shows that only 88 units per c.c. of timothy was required to achieve the same degree of neutralization, which would indicate that, toward this particular serum, timothy is about fifty times as active as Bermuda. The reciprocal tests (columns 3) show that Bermuda did not neutralize its sites appreciably to timothy, while timothy almost completely neutralized its sites to Bermuda. Timothy and Bermuda are, therefore, not neutralizing the same thing.

This is likewise true with the serum of BR who is predominantly Bermuda-sensitive (Table III). Here also the first test, made by the injection of serum together with the serial dilutions of the pollen (right and left columns 1) can be disregarded. In the re-tests (columns 2) if 7 and 15 is the last significant reaction with Bermuda and 6 and 15 is the last with timothy, it means that 10 units of timothy with this serum will neutralize as much reagin as 810 units of Bermuda. Or that timothy neutralizes about 81 times as much of its reagin as does Bermuda, in spite of the fact that this is predominantly a Bermuda serum. Moreover, the reciprocal tests (columns 3) show that timothy in spite of its superior neutralizing capacity did not noticeably neutralize its sites to Bermuda, while the weaker Bermuda did neutralize its sites to timothy. The only possible explanation of this apparent contradiction is again that two antigens in the two different pollens are neutralizing two different reagins in the two sera.

There are therefore two antigens and two reagins involved in these

## TIMOTHY VERSUS BERMUDA GRASS—WODEHOUSE

TABLE III. TIMOTHY VERSUS BERMUDA IN NEUTRALIZING BR SERUM. REACTIONS OF NORMAL SITES TO MIXTURES OF BR SERUM AND DILUTIONS OF TIMOTHY AND BERMUDA, AND HOMOLOGOUS AND RECIPROCAL RETESTS

Clxvi	Left Timothy						Right Bermuda						
Tim. Units	1. Test BR+Tim.		2. Retest Tim. 500 u		3. Reciproc. B'da 4,000 u		1. Test BR+B'da		2. Retest B'da 4,000 u		3. Reciproc. Tim. 500 u		B'da Units
p. c.c.	W	E	W	E	W	E	W	E	W	E	W	E	p. c.c.
0.0	8	0	7	10	10	35	12	0	11	50	6	0	0.0
1.1	15	25	8	15	10	35							
3.3	12	20	7	15	12	35							
→10	12	25	→6	15	12	35	12	30	9	45	6	0	10
30	12	20	5	10	13	35	10	40	9	40	6	0	30
90	12	0	6	0	13	40	12	50	8	40	5	0	90
							13	25	8	20	6	0	270
							13	30	→7	15	5	0	810←

Test: 0.05 c.c. BR serum undiluted + serial dilutions of timothy (left) and of Bermuda (right), *in vitro* one hour room temperature.

Retest: 0.01 c.c. timothy 500 u., Bermuda 4,000 u.

Reciprocal: 0.01 c.c. Series: 3x.

TABLE IV. REACTIONS OF SENSITIZED SITES TO TIMOTHY AND TO BERMUDA GRASS, AND TO THEIR RETESTS AND RECIPROCAL TESTS.

Clxlii	1. Test		2. Retest			3. Reciprocal Test		
	W	E		W	E	W	E	
JB Serum 1:70*								
Tim. 100 u	9	55	Tim. 300 u	6	0	7	0	B'da. 1,500 u
B'da. 1,500 u	8	45	B'da. 2,500 u	5	0	8	40	Tim. 100 u
BR Serum 1:5								
Tim. 100 u	6	40	Tim. 300 u	4	0	11	60	B'da. 1,500 u
B'da. 1,500 u	11	60	B'da. 2,500 u	6	8	6	0	Tim. 100 u
Normal Serum 1:1								
Tim. 100 u	6	0	Tim. 300 u	6	0	6	0	B'da. 1,500 u
B'da. 1,500 u	6	0	B'da. 2,500 u	6	0	5	0	Tim. 100 u

Sensitized: 0.05 c.c. sera.

Tested: 0.01 c.c., intervals twenty-four hours.

\*Diluted with normal serum 1:5.

reactions. And, since both pollens react with both sera, it necessarily follows that each pollen contains two separate antigens corresponding to each of the two sera, and each serum contains two reagins corresponding to each of the two pollens.

This thesis is put to the test in the experiment shown in Table IV. This is a comparison of the *in vivo* neutralization of the two sera JB and BR by extracts of timothy and Bermuda, after their concentrations had been adjusted in the direction of equalizing the JB serum to the BR serum in terms of their reaction with timothy, and of equalizing the Bermuda extract to that of timothy in terms of their reaction with JB serum.

Thus, the sites which were sensitized with JB and BR sera are at dilutions of 1:70 and 1:5, respectively, and are tested with timothy and Bermuda extract at concentrations of 100 and 1,500 N units, respectively.

At the dilutions and concentrations so chosen, good positive reactions not too different in intensity were obtained, which fully met the requirements of the experiment (column 1). In passing though, it is worth noticing that with JB serum, timothy gave a larger reaction than Bermuda in the concentrations used, but that with BR serum the reverse was the case; also that timothy with JB gave a stronger reaction than with BR in spite of the fact that the former serum is fifteen times as dilute, and that with Bermuda the reverse is the case. It is these reversals that make accurate potency adjustments impossible.

However, that the adjustments were close enough for the purposes of the experiment is seen from the retest (column 2) made the next day. In this the same extracts were used, but in greatly increased concentrations, to be sure of detecting and, if present, completely neutralizing any remaining reagins at the sites, that these antigens can neutralize. These retests show that all except the Bermuda-BR site had been completely desensitized to their homologous antigens by the first test. Also, since the Bermuda reaction of 6 and 8 is a borderline reaction of doubtful significance, its site was surely desensitized by the second test.

When the reciprocal tests were done on these sites the next day (column 3) it was found that with JB serum timothy had desensitized its site to Bermuda, but that Bermuda had not materially desensitized its site to timothy. The opposite was found to be true with BR sites. Here Bermuda completely desensitized its site to timothy, but timothy did not materially desensitize its site to Bermuda. In brief, timothy easily and completely desensitizes JB sites to both antigens but cannot desensitize BR sites to Bermuda, and Bermuda easily and completely desensitizes BR sites to both antigens but cannot desensitize JB sites to timothy. One perhaps should add, *under the conditions of the experiment*. One condition of the experiment is that the antigen used is several or many times the neutralizing concentration required for its homologous reagin. It should be noted, however, that the timothy reaction following two Bermuda tests is somewhat smaller than the timothy reaction in the first place, in spite of the fact that the smaller had the advantage of the greater time interval. The Bermuda reaction following two timothy tests was the same as the Bermuda reaction in the first place but would have been expected to be larger, owing to the advantage in time interval. The margin in either case is small, but seems to demonstrate a slight heterologous activity going along with the homologous.

A possible explanation of the facts so far known is expressed in the accompanying diagram (Figs. 2 and 3). The reagins are indicated in dark circles and the antigens in light circles.

Timothy extract possesses two antigens—timothy antigen which is pre-

dominant, and Bermuda antigen, which is subordinate—indicated by large and small light circles. JB serum possesses two reagins, timothy reagin, which is predominant, and Bermuda reagin, which is subordinate, represented by the large and small dark circles.

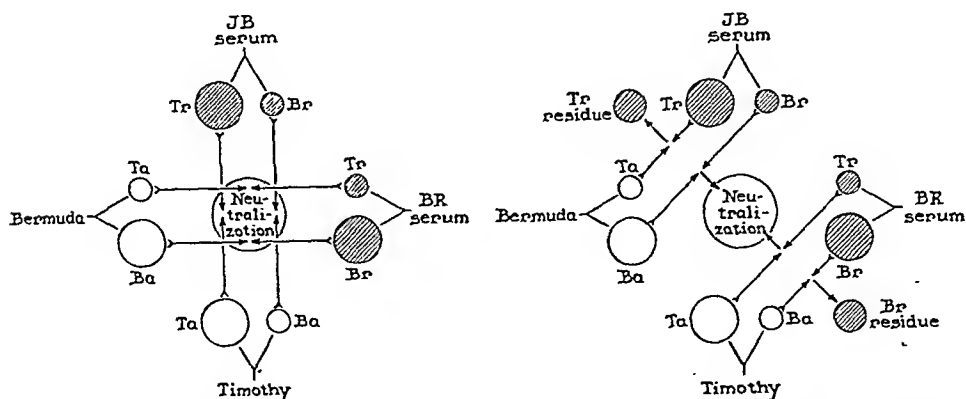


Fig. 2. (left) Diagram of homologous pollen reactions. Fig. 3. (right) Diagram of heterologous pollen reactions. In both figures Tr indicates timothy reagin, Br Bermuda reagin, Ta timothy antigen, and Ba Bermuda antigen.

When a site which is sensitized with JB serum is tested with timothy (indicated vertically through the diagram, Figure 2) the predominant timothy antigen neutralizes the predominant timothy reagin, and the subordinate Bermuda antigen neutralizes the subordinate Bermuda reagin. Such a site is thereafter inactive to both timothy and Bermuda. Or, if a site which is sensitized to BR serum is tested with Bermuda (indicated horizontally through the diagram, Figure 2), the Bermuda and timothy antigens neutralize their corresponding reagins and that site is thereafter inactive to both pollens. These are homologous reactions characterized by complete neutralization of the sites.

On the other hand, if a JB site is tested with Bermuda (indicated obliquely in Figure 3 from left to top) the predominant Bermuda antigen neutralizes the subordinate Bermuda reagin, but the subordinate timothy antigen does not appreciably affect the predominant timothy reagin; most of it is left over (Tr residue) leaving the site still active to timothy, though desensitized to Bermuda.

In the same way if a BR site is tested with timothy (indicated obliquely in Figure 3 from bottom to right) the primary timothy antigen will neutralize the secondary timothy reagin, but the secondary Bermuda antigen will not materially affect the primary Bermuda reagin. Most of it will remain at the site (Br residue) keeping this site active to Bermuda, though desensitized to timothy.

These two latter reactions are heterologous and are characterized by the neutralization of a subordinate reaginic factor leaving the site still active to its predominant antigenic factor.

Though it is always unsafe to generalize from a few specific examples, we can at least hazard a guess as to the antigenic structure of the various hay-fever pollens. These experiments seem to indicate that each species of pollen possesses a predominant antigen which generally, if not always, is accompanied by one or more subordinate antigens. And each pollen-sensitive serum possesses a predominant reagin, generally, if not always, accompanied by one or more subordinate reagins. These do not necessarily correspond to the subordinate antigens accompanying the predominant antigen of the pollen which caused the owner of the serum to have hay fever. They correspond rather to the predominant antigens of pollens which secondarily may influence the patient's hay fever.

Some preliminary experiments have already been done which show that the subordinate reagins need not represent antigens of the same biological group. JB serum was found to sensitize skin sites to pigweed and black walnut, pollens which are totally unrelated to each other or to timothy and Bermuda. Timothy, however, to which this serum exhibited the predominant sensitization, was found to desensitize JB sites to both of these as well as to Bermuda. But not any of these will desensitize the sites to timothy, though they do to each other. Similarly, it was found that BR serum will sensitize sites to slender ragweed, which is totally unrelated to Bermuda and timothy. Nevertheless, Bermuda, which in this case determines the predominant sensitization, will desensitize the sites to slender ragweed but the latter will not desensitize them to the predominant Bermuda, though it does to the subordinate timothy.

These observations are not entirely unique. Others have observed a multiplicity or polyvalency of reagins in various forms.

The almost fortuitous distribution of these reagins suggests at least a partial analogy with the synergens of Clarke and Bolden (1937). They say, "Careful study of persons suffering from hay fever will show that inhalation of substances other than the major pollen, which determines the duration of the symptoms, will greatly aggravate the disease. The word synergy is suggested for this combined action."

Though these authors are speaking only of antigens, presumably each synergen must be represented by a reagin in the patient's serum to be effective. They emphasize the fact that while there may be major and minor synergens, their clinical manifestation is due to the combined action of a number rather than to the intensive action of any single one. This, at present, seems to be an important difference between synergens and our predominant and subordinate antigens and reagins. The subordinate are accessory to, rather than co-ordinate with, the primary antigens or reagins.

Similarly, Walzer (1940) referring to some recent studies of Harten and Bowman, observed, "It was found that of five hundred patients with frank pollinosis residing in this city [New York] all of them, with only six exceptions, showed positive cutaneous reactions of varying degree to

representatives of all four groups of ubiquitous pollen—namely, timothy, ragweed, plantain and trees. . . . These positive reactions were specific as they were transferable to normal skin in ninety-seven per cent of trials. . . . Two sera obtained from hay fever cases in Hawaii, where the pollinating flora is different from ours; showed a lack of uniformity when tested for the presence of reagins for the aforementioned four pollen groups.”

The specificity of the accessory reagins and antigens observed by these investigators is also a salient characteristic of our subordinate reagins and antigens, and prevents them from being confused with a common antigen such as the Frossman antigen, or heterogenetic antigens, as commonly understood.

Coca and Grove (1925) experimenting with the serum of a patient with hay fever from spring grasses, found that its sensitized sites could be desensitized by timothy against June grass, and reverse. Timothy could also desensitize them against orchard grass, but not the reverse; orchard grass could not desensitize against timothy. Undoubtedly orchard grass was a subordinate sensitization in this serum, while timothy and June grass were predominant and equal, bearing the same relation to each other that the two ragweed sensitizations appear to do in most cases. In this connection it is worth noticing that the four grasses in question are very closely related, and the donor of the serum had undoubtedly been exposed to the pollen of all of them though probably in different degrees.

More closely parallel with the results of the present investigation are those of these investigators with the serum of a patient with asthma from cotton and kapok seeds. Sites sensitized by this serum could be desensitized by cotton against kapok, but not the reverse. In this serum cotton was the dominant sensitization and kapok subordinate. It is conceivable that another cotton-kapok allergic might be found in which kapok is the predominant sensitization with cotton subordinate. Such an event would make the situation almost exactly parallel with our results with timothy and Bermuda grass pollens.

In this connection it is interesting to notice that cotton belongs to the *Malvaceae* while kapok belongs to the *Bombacaceae*. Though the families are undoubtedly closely related, this classification suggests a much greater genetic difference than exists among the grasses.

That cross reactions, such as we are dealing with, are not necessarily confined to one family or even to related families has been further brought out by Cooke (1944). He reports a study of four sera capable of sensitizing to ragweed, amaranth, chenopod, cocklebur, marsh elder, sagebrush and Russian thistle. These sera he tested by means of the *in vitro* neutralization technique, in which the sites are sensitized by mixtures of the antigen and sensitizing serum. He found that with two of the sera, ragweed would neutralize to all of the sensitizations; with one of them to ragweed alone; and with the fourth serum ragweed failed to

neutralize the site to itself but did to amaranth and chenopod. Presumably in the first two sera ragweed was the predominant sensitization, while in the third it was only a subordinate. In the fourth the ragweed was obviously used at a concentration too weak to neutralize its own reagin; but the test is interesting in suggesting that a partial neutralization of a predominant reagin, which in this case the ragweed probably was, may result in the neutralization of one or more of the subordinates.

Cooke also reports on a serum capable of twenty-two specifically different sensitizations, representing all the major groups of pollens and several other allergens. Using, as before, the *in vitro* neutralization technique, he found that ragweed would neutralize this serum in all of its sensitizations, except plantain and sorrel dock, but including cottonseed, orris, flaxseed, lycopodium, alternaria and pyrethrum. Most of the subordinates were found to neutralize to other subordinates but never to the predominant ragweed.

From the foregoing, it seems to us that any satisfactory approach to the potency standardization of allergenic extracts must take into consideration the subordinate antigens as well as the predominant. It would seem also that treatment should be designed to strike at the predominant sensitization which carries with it most or all of the subordinate rather than attempting to be all-inclusive. However, this will have to await further serological investigation, for it by no means follows that the development of immunity is parallel to the neutralization of reagins.

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# THE CHEMICAL AND IMMUNOLOGIC BASIS OF ORAL POLLEN PROPEPTAN THERAPY IN HAY FEVER

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WHILE subcutaneous hyposensitization with pollen extracts generally constitutes a dependable method of dealing with pollinosis, treatment involving injections has a number of distinct disadvantages. Persons who are needle-shy, notably children, often refuse to submit to treatment; individuals who are very busy or who travel a great deal find it most inconvenient to visit the physician twenty or more times; many cannot afford the cost of such treatment; and there is always the possibility of some untoward reaction (systemic symptoms or even shock) following an injection. Although an experienced physician can reduce the number and severity of such occurrences they cannot be entirely avoided.

The most successful alternative to the injection method has been the administration of pollen by mouth. Numerous investigators have reported encouraging results obtained with this method. However, crude pollens are likely to cause distressing gastrointestinal symptoms as a result of absorption of the undenatured antigen contained in the pollen. For this reason, the senior author,<sup>4</sup> in 1931, introduced oral therapy with pollen digests, termed pollen propeptans.

## CHEMISTRY OF POLLEN PROPEPTANS

Pollen propeptans are derived from the individual pollen through digestion by hydrochloric acid, pepsin, and, in some instances, with trypsin.

This procedure deprives the pollen of their native protein but not of their type-specificity. These preparations contain all the protein cleavage products and protein derivatives, such as proteoses, peptones, simple peptids and amino acids. On the other hand, as demonstrated by tests with 10 per cent sulfosalicylic acid and 10 per cent trichloroacetic acid, pollen propeptans\* do not contain appreciable amounts of native protein or metaprotein.

While food propeptans have proven most effective when hydrolysis with pepsin was followed by a very slight degradation by means of trypsin, resulting in digests composed of approximately 70 to 80 per cent proteose-N and 10 to 15 per cent peptone-N (Urbach, Jaggard and Crisman<sup>6</sup>), extensive animal and clinical research has shown that in dealing with pollens, conditions vary according to the origin of the pollen. Thus, grass pollen digests have the best protective action when subjected to prolonged hy-

From the Department of Allergy, Jewish Hospital. Expenses for this work were defrayed in part by a grant from the Allergy Research Foundation, Inc., Philadelphia, Pennsylvania.

Doctors Jaggard and Crisman are Associate Fellows of the American College of Allergists. \* Pollen propeptans are in themselves free from native protein. However, for reasons stated elsewhere in this paper, glycyrrhiza is added to the propeptans intended for therapeutic use. This saponin contains 1.4 per cent protein nitrogen. Pure pollen propeptans for experimental purposes will be supplied by Dalare Associates, 2300 Locust Street, Philadelphia 3, Pennsylvania, on request.



# ORAL POLLEN PROPEPTAN THERAPY—URBACH ET AL

TABLE I. CHEMICAL COMPOSITION OF REPRESENTATIVE POLLEN AND FOOD PROPEPTANS.

	Dwarf Ragweed	Cocklebur	Timothy	Egg
Type of Digestion	Long Acid and Long Alkaline Digestion	Long Acid and Long Alkaline Digestion	Long Acid Digestion	Long Acid and Short Alkaline Digestion
Total N	4.40	6.10	3.1	9.15
Water Soluble N	3.51	5.71	3.1	9.15
Water Insoluble N	0.89	0.39	none	none
Acid Precipitate N	none	none	none	none
Proteose N	1.42	0.74	1.74	6.90
Peptone N	0.53	2.15	0.79	0.89
Subpeptone and Simple Peptid N	0.74	1.22	0.42	0.14
Amino Acid N	0.82	1.60	0.15	1.22
Percentage of Soluble Nitrogen as: Proteose	40.5	13.0	56.0	75.3
Peptone	15.1	37.6	25.4	9.7
Subpeptone and Simple Peptid	21.0	21.3	13.7	1.6
Amino Acid	23.4	28.1	4.9	13.4

drochloric-pepsin hydrolysis alone; while ragweed and cocklebur pollen, on the other hand, require prolonged acid and alkaline digestion with pepsin and trypsin.

Table I presents representative examples of the chemical composition of ragweed, cocklebur, timothy and egg propeptans. The protein cleavage products were analyzed according to the procedure described by Wasteneys and Borsook.<sup>9</sup>

The exact degree of digestion required in the preparation of pollen propeptans in order to obtain the best therapeutic results was determined in a series of animal experiments. They indicated that grass pollen propeptans are most efficacious when they contain some 80 per cent proteoses and peptones, while ragweed and cocklebur propeptans afford maximal protection when these degradation components comprise no more than 50 to 55 per cent of the total preparation. A pollen propeptan is considered satisfactory when it protects a highly sensitized guinea pig against a multiple lethal dose of pollen antigen. In addition, the type of immunologic protection involved, i.e., hyposensitization or temporary deallergization, was determined by performing the Schultz-Dale and lung perfusion tests; positive tests denote the presence, negative test the absence, of antibodies.

## IMMUNOLOGIC PROPERTIES OF POLLEN PREPARATIONS

Although stripped of native protein, the pollen propeptans retain their type-specific immunologic properties, at least as far as their reactivity in

the Prausnitz-Kustner reaction is concerned. This is best demonstrated by the positive passive transfer of pollen hypersensitiveness, pollen propeptans being used instead of the pollen proper in the test.

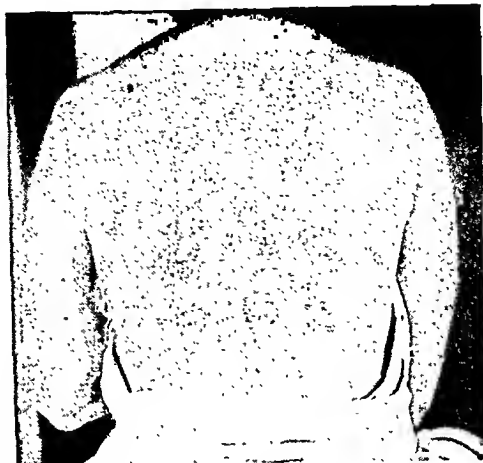


Fig. 1. Passive transfer of hypersensitiveness to ragweed pollen by use of ragweed pollen propeptan as antigen. Reactions, reading from top, left to right, are: (a) patient's serum and ragweed pollen, (b) patient's serum and ragweed pollen propeptan, (c) patient's serum and saline; below, left to right, (d) control serum and ragweed pollen, (e) control serum and ragweed pollen propeptan, and (f) control serum and saline.

Thus, in Figure 1, a recipient exhibits a reaction to ragweed pollen propeptans which is as strongly positive as is his reaction to ragweed pollen itself.

In the course of their study of the immunologic and therapeutic properties of the pollen propeptans, the present writers administered these preparations to animals which had been highly sensitized, in one of three ways: intravenously, orally, or bronchially. By bronchial administration we mean the exposure of the bronchial mucosa to the antigen by ordinary inhalation by the animal in a specially constructed inhalation chamber. The shock dose was administered either intravenously or bronchially. The great majority of animals had been sensitized to pollen; consequently, pollen propeptans were given for protection, and pollen to elicit the shock reaction. In some instances, the animals were sensitized to pollen propeptans; here protection was tried with pollen and the appropriate pollen propeptans was used to elicit shock. Table II presents the variations.

#### TECHNIQUE

For each experiment, we used twenty virgin guinea pigs weighing an average of 250 gm. and kept throughout on an acidifying diet, consisting of 7 gm. of rolled oats, 5 gm. of whole wheat bran, and 10 gm. each of potatoes, beets and hay, daily.

This type of dietary is necessary, because it is difficult to sensitize animals on a diet of green fodder, which is alkalinizing (Sulzberger and Mayer<sup>3</sup>). The animals can be readily allergized to pollen by the parenteral

TABLE II. OUTLINE OF EXPERIMENTS INDICATING TYPE OF ANTIGEN, KIND OF PROTECTION AND MODE OF SHOCK DOSE.

Guinea Pigs Sensitized to Ragweed Pollen	Protection with Ragweed Pollen Propeptan	Shock Dose with Ragweed Pollen
"	intravenously	intravenously
"	intravenously	bronchially
"	bronchially	intravenously
"	bronchially	bronchially
"	orally	intravenously
"	orally	bronchially
Guinea Pigs Sensitized to Ragweed Pollen	Protection with Ragweed Pollen Extract	Shock Dose with Ragweed Pollen
"	bronchially	bronchially
"	orally	bronchially
Guinea Pigs Sensitized to Ragweed Pollen	Protection with Cocklebur Pollen	Shock Dose with Ragweed Pollen
"	orally	intravenously

route, the sensitization becoming manifest somewhere between the forty-third and the fifty-fifth day following a subcutaneous injection of 2.0 c.c. of a 5 per cent alum-precipitated pollen extract.

#### PREPARATION OF ALUM-PRECIPITATED RAGWEED EXTRACT

This method was introduced by Harrison<sup>2</sup> and successfully employed by Caulfeild.<sup>1</sup> We used the following simplified procedure:

Five grams of ragweed pollen are extracted with 95 c.c. of distilled water for twenty-four hours with continuous agitation. The pollen extract is then rendered sterile by passing through a "Seitz" filter. A 10 per cent solution of potassium alum [ $\text{Al}_2(\text{SO}_4)_3 \cdot \text{K}_2\text{SO}_4 \cdot 24\text{H}_2\text{O}$ ] is added to the pollen extract to give a final concentration of 1 per cent potassium alum. Adjustment of the reaction to pH 7.0 causes the appearance of a copious precipitate. The mixture is allowed to stand twenty-four hours. For purposes of sensitizing, this neutral alum-treated pollen extract is well shaken, and 2.0 c.c. of the suspension are administered subcutaneously.

Each individual batch of propeptan must be carefully checked to rule out any possible toxic action or any tendency to evoke a nonspecific reaction

on the uterus in the Schultz-Dale test. A preparation may be classified as non-toxic when an intravenous injection of 4.0 c.c. of a 10 per cent digest is tolerated perfectly by the animal.

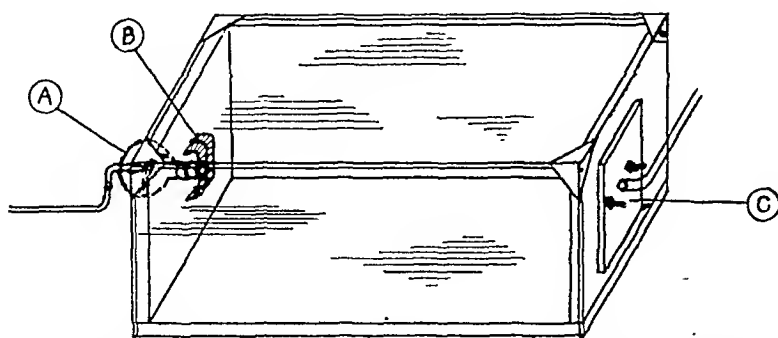


Fig. 2. Chamber used for the inhalation experiments with dwarf ragweed pollen extracts. (A) glass atomizer, (B) copper screen, (C) hermetically sealed opening.

While the minimal lethal dose (M.L.D.) of pollen extracts varies somewhat, depending on the animal's weight and strain as well as on its diet and the season, it is generally in the neighborhood of 0.1 c.c. of a 5 per cent extract when the intravenous route is used, and a ten-minute bronchial exposure to a 5 per cent extract by the bronchial route.

#### DESCRIPTION OF CONSTRUCTION OF THE INHALATION CHAMBER

The apparatus used in the inhalation experiments (Fig. 2) is rather simple in construction. It consists essentially of an air-tight chamber of the following dimensions: 10 cm. in height, 40 cm. in length, and 30 cm. in width. The top and one side of the box are constructed of clear, heavy glass, so that the animals may be observed during the course of the experiment.

The animals are introduced into the chamber through an opening in the side, so constructed that it can be hermetically sealed.

The atomizer, which is entirely of glass (vaponephrine atomizer), is introduced into the interior of the chamber through a sealed opening at one end of the apparatus. A metal screen is used as a guard for the nozzle of the atomizer, in order to prevent direct contact of the animals with the spray, and thus to insure uniform dosage of the various animals. The air pressure required to force the atomized suspension of antigen into the chamber is supplied by means of an electric air-pump, equipped with a device for controlling the pressure to any desired degree (about 10 pounds).

The outlet is constructed at the opposite end of the chamber, and is covered with a 200-mesh screen. A suitable exhaust tube is attached to the outlet-opening.

When animals are sensitized by the oral route this is facilitated considerably by the addition of the saponin glycyrrhiza to the crude pollen. Glycyrrhiza greatly increases the allergizing properties of the antigen be-

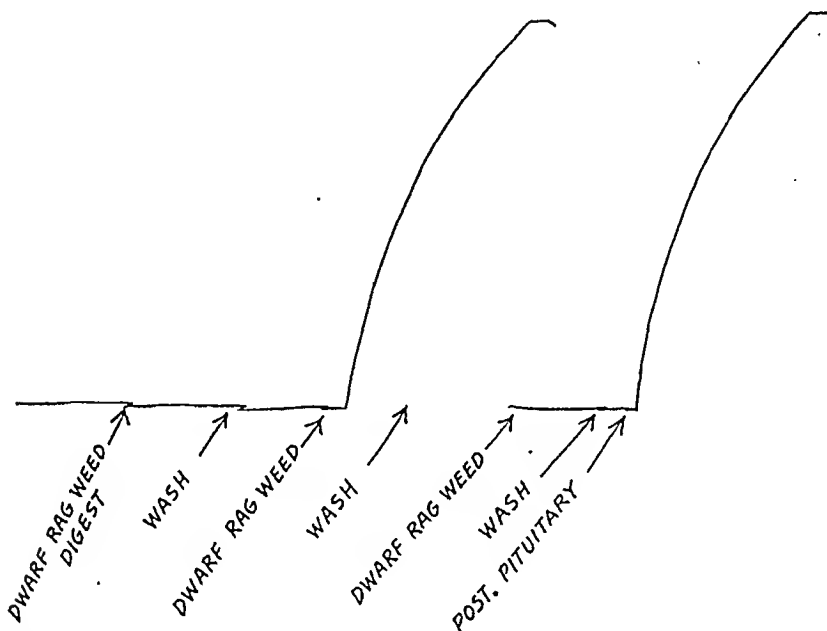


Fig. 3. Schultz-Dale test performed upon the uterus of a guinea pig, allergized to dwarf ragweed pollen by subcutaneous injection of dwarf ragweed pollen extract precipitated with alum. The animal died as the result of a lethal intravenous injection of dwarf ragweed pollen extract. There was no reaction upon the addition of dwarf ragweed pollen digest (dwarf ragweed pollen propeptan). A positive reaction followed the addition of dwarf ragweed pollen extract indicating the presence of antibodies. No reaction followed a second addition of dwarf ragweed pollen extract, proving that the preceding reaction was specific. A final addition of posterior pituitary extract was made as a check upon the sensitivity of the uterus.

cause of better resorption resulting from its action in dissolving intestinal mucus (Urbach et al.<sup>7</sup>).

#### ORIGINAL EXPERIMENTS

*Experiment 1.*—Twenty guinea pigs were allergized to dwarf ragweed pollen by subcutaneous injection of 2.0 c.c. of a 5 per cent dwarf ragweed pollen extract, precipitated with 1 per cent alum. Fifty days later, 0.1 c.c. of a 1 per cent dwarf ragweed pollen extract, administered intravenously, evoked a slight reaction. However, when 0.1 c.c. of a 5 per cent dwarf ragweed pollen extract was injected, the animal died in about six minutes, exhibiting anaphylactic symptoms of the utmost severity. The Schultz-Dale test was positive (Fig. 3). The lung, at autopsy, showed maximal inflation (Fig. 4).

This experiment demonstrates that the minimal lethal dose is 0.1 c.c. of a 5 per cent ragweed pollen extract, administered intravenously.

*Experiment 2.*—Seventeen guinea pigs were allergized to dwarf ragweed pollen by subcutaneous injection of 2.0 c.c. of a 5 per cent dwarf ragweed pollen extract precipitated with 1 per cent alum. From forty-three to forty-seven days later, the animals were exposed, in the inhalation chamber, to a vapor of a 5 per cent "Seitz" filtered dwarf ragweed extract. Six of the guinea pigs died within three to ten minutes in acute anaphylactic shock.

Four animals exhibited most severe anaphylactic symptoms (violent gagging, falling to the side), but recovered. Six suffered violent asthmatic attacks, and only one presented asthmatic symptoms, which might be described as slight. Every sur-

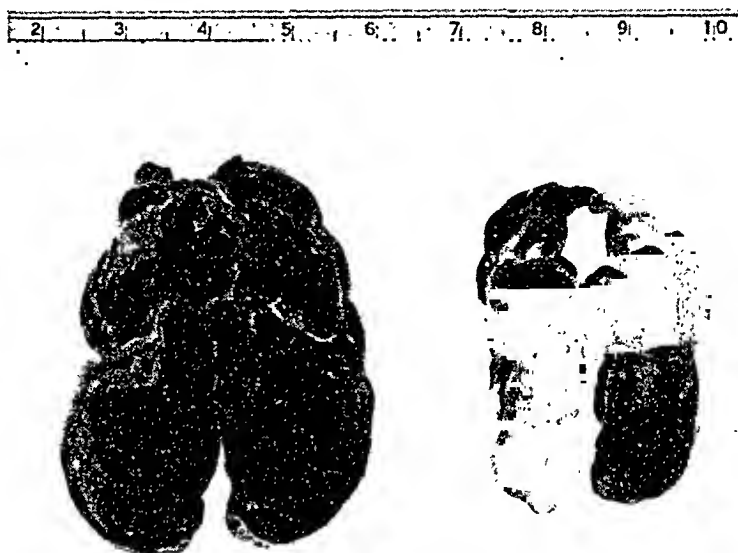


Fig. 4. The lung of a guinea pig allergized to dwarf ragweed pollen by subcutaneous injection of dwarf ragweed pollen extract precipitated with alum. The animal died as the result of a lethal intravenous injection of dwarf ragweed pollen extract. The lung (left), at autopsy, showed maximal inflation. A control lung of a non-allergized animal of the same weight (right), showed no inflation.



Fig. 5. Lung perfusion test performed upon the lung of a guinea pig allergized to dwarf ragweed pollen by subcutaneous injection of dwarf ragweed pollen extract precipitated with alum. The animal was exposed in the inhalation chamber, to a vapor of dwarf ragweed extract. The lung (left) showed extreme inflation. A control lung of a non-allergized animal of the same weight (right) showed a negative reaction when exposed to the same treatment.

viving animal was sacrificed within a half hour. In each case, the Schultz-Dale test was positive and the lung showed marked inflation (Fig. 5).

While we have been unable to determine a uniform minimal lethal dose in so far as bronchial exposure to pollen extract is concerned, the overwhelming majority of our animals exhibited severe or fatal manifestations of anaphylaxis when exposed for ten minutes to a 5 per cent dwarf ragweed pollen extract.

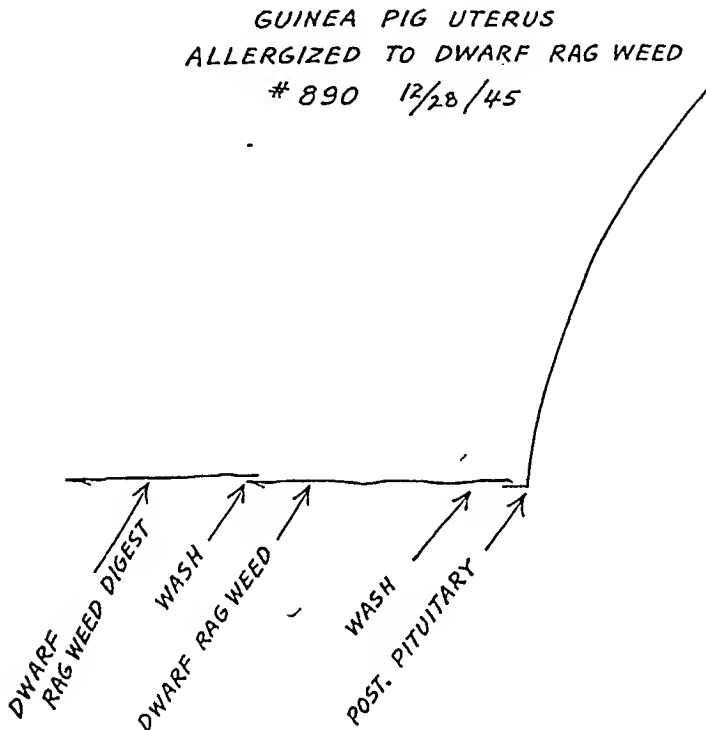


Fig. 6. Schultz-Dale test performed upon the uterus of a guinea pig allergized to dwarf ragweed pollen by subcutaneous injection of dwarf ragweed pollen extract precipitated with alum. Following a treatment with intravenous skeptophylactic injections of dwarf ragweed pollen digest (dwarf ragweed pollen propeptan), the animal was able to survive a twenty times minimal lethal intravenous shock dose of dwarf ragweed pollen extract. The animal was killed two hours after the last injection. There was no reaction upon the addition of dwarf ragweed pollen digest or dwarf ragweed pollen extract, indicating the absence of antibodies.

*Experiment 3.*—Guinea pigs were allergized to dwarf ragweed pollen by subcutaneous injection of 2.0 c.c. of five per cent dwarf ragweed pollen extract precipitated with 1 per cent alum. Forty-five days later the following treatment was instituted.

*Treatment:* Five intravenous injections of dwarf ragweed digest at ten-minute intervals:

Injection 1.—Pollen digest representing 1.0 mg. of soluble nitrogen—No reaction.

Injection 2.—Pollen digest representing 2.5 mg. of soluble nitrogen—No reaction.

Injection 3.—Pollen digest representing 5.0 mg. of soluble nitrogen—Bristling.

Injection 4.—Pollen digest representing 10.0 mg. of soluble nitrogen—Bristling.

Injection 5.—Pollen digest representing 20.0 mg. of soluble nitrogen—Bristling.

Two hours later: Intravenous shock dose of five per cent dwarf ragweed pollen extract at five-minute intervals:

Injection 1.—1 M.L.D.—No reaction.

Injection 2.—2.5 M.L.D.—No reaction.

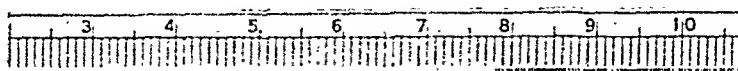


Fig. 7. Lung perfusion test performed upon the lung of a guinea pig allergized to dwarf ragweed pollen by subcutaneous injection of dwarf ragweed pollen extract precipitated with alum. Following a treatment of intravenous skeptophylactic injections of dwarf ragweed pollen digest, (dwarf ragweed pollen propeptan), the animal was able to survive a twenty times minimal lethal intravenous shock dose of dwarf ragweed pollen extract. The animal was killed two hours after the last injection. The lung (left) showed no inflation, indicating the absence of antibodies. A control lung of a non-allergized animal of the same weight (right) showed a negative reaction in the lung perfusion test.

Injection 3.—5 M.L.D.—Bristling and diaphragmatic breathing.

Injection 4.—10 M.L.D.—Bristling and diaphragmatic breathing.

Injection 5.—20 M.L.D.—Bristling and diaphragmatic breathing.

Animals killed two hours after the last shock dose:

Schultz-Dale Test—Negative (Fig. 6).

Lung perfusion Test—Negative (Fig. 7).

Experiment 3 demonstrates that guinea pigs are able to withstand twenty M.L.D. following skeptophylactic treatment in the form of mounting doses of ragweed pollen propeptan administered intravenously at ten-minute intervals. The fact that both the Schultz-Dale test (Fig. 6) and the lung perfusion test (Fig. 7) were negative, demonstrating the absence of antibodies in the two most important shock organs of the guinea pig (uterus and lung), would seem to indicate that this immunologic procedure (skeptophylactic) induced at least a temporary state of de-allergization.

*(To be Concluded in May-June Issue)*



# USE OF CROTALIN IN THE PREVENTION OF ANAPHYLACTIC SHOCK IN GUINEA PIGS

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THE stimulating action of snake venoms on smooth muscle<sup>7</sup> resembles greatly the action of histamine on smooth muscle. Feldberg and Kellaway<sup>5</sup> have, in fact, demonstrated that, following the action of snake venom, histamine is released from the perfused organs of guinea pigs, dogs and cats. Code,<sup>1</sup> Schild<sup>12</sup> and others have demonstrated that histamine is released from the various shock organs during anaphylactic shock. It ought to be mentioned that the action of trypsin in producing shock, also resembles anaphylactic shock,<sup>4,9</sup> and that, apparently, the release of histamine again<sup>8</sup> is the responsible mechanism.

Spangler,<sup>13,14</sup> who has long advocated the use of crotalin (rattlesnake venom) in certain allergic disorders and especially in epilepsy, has suggested that the favorable action of the drug in his cases was essentially due to a non-specific protein action. The known release of histamine into the organism, following the injection of snake venom, suggested to the author that the favorable clinical results obtained by Spangler through the use of crotalin, might, possibly, be due to the release of histamine following each injection of the snake venom, with the subsequent development of a histamine tolerance, and any benefits which may accompany such a tolerance.<sup>3</sup> If this theoretical concept be tenable, then small doses of crotalin injected into test animals should be capable of releasing histamine with a development of a histamine tolerance in the animals. The development of a histamine tolerance should help prevent some of the effects of anaphylactic shock. Success in the majority of a fairly large group of test animals would lend some significance to the theory attempting to explain the results. Likewise, if a single injection of crotalin were given test animals a day before the anaphylactic dose of antigen was given, insufficient time should have elapsed for the animals to develop a histamine tolerance. Such animals should not be protected by the crotalin from the effects of anaphylaxis, if the theory expressed is to remain tenable. The following experiments were performed to test these concepts.

## PROCEDURE AND RESULTS

Ten guinea pigs, average weight 300-400 gm., serving as controls, were sensitized to normal horse serum by means of an intra-abdominal injection of 1 ml. of a 1 to 10 dilution of horse serum. Fourteen days later the animals were injected intravenously with a 1 ml. dose of a 1 to 2 dilution of normal horse serum. All ten animals promptly went into anaphylactic shock and died. The 1 to 2 dilution of horse serum, in previous experiments, has been found universally fatal for guinea

## ANAPHYLACTIC SHOCK—FRANK

TABLE I. CROTALIN PRÉTREATMENT IN ANAPHYLACTIC SHOCK

Group	Number of Animals	Top Dose of Crotalin	Total Dose of Crotalin	Total Length of Treatment	Day Sensitized	Results		Comment on Living
						Living	Dead	
I	5	.036 mg.	.575 mg.	24 days	10	4	1	1 staggered 1 convulsions 1 mod. dyspnea
II	5	.005 mg.	.15 mg.	28 days	14	3	2	2 sl. dyspnea
III	8	.036 mg.	.677 mg.	24 days	10	7	1	4 mod. dyspnea 3 sl. dyspnea
IV	5	.113 mg.	1.12 mg.	16 days	3	1	4	severe dyspnea
V	5	.033 mg.	.455 mg.	14 days	1	4	1	2 mod. dyspnea
VI	8	.65 mg.*	.65 mg.	1 day	1	4	4	4 mod. dyspnea
Total	36					23	13	
VII	10	.65 mg.†	.65 mg.	1 day	1	0	10	

\*Dose given on second day.

†Dose given on fourteenth day, the day before shock dose of antigen.

pigs of this size. Therefore, fatality is used as the critical point in the symptoms of anaphylaxis.

Forty-eight guinea pigs, of the same weight as the controls, were divided into seven uneven groupings. Groups I, II, III, and IV were pretreated daily with intra-abdominal injections of increasing doses of crotalin (*crolus horridus*) for three to fourteen days, at which time the animals were sensitized to horse serum, as in the controls, with a 1 ml. injection of a 1 to 10 dilution. Treatment with the snake venom was continued daily with the highest dose attained at the time of sensitization, for an additional fourteen days, at which time a 1 ml. dose of a 1 to 2 dilution of horse serum was injected intravenously. Group V was first sensitized to horse serum, in the same manner as the other animals. On the next day and for fourteen successive days, the animals received a constant small dose of crotalin intra-abdominally. On the fifteenth day they were shocked with antigen, in the manner of the other animals. Group VI was similarly sensitized on the first day, and on the next day, a single large dose of crotalin, equal to or greater than the sum of all the small doses given to the animals in Groups I, II, III and V, was given intra-abdominally. On the fifteenth day the animals were shocked with horse serum, as with the other animals. Group VII was also sensitized on the first day. No treatment was given until the fourteenth day, at which time a single large dose, similar to that given to Group VI, was given intra-abdominally. On the fifteenth day the animals were shocked with horse serum intravenously. The results of these procedures are shown in Table I.

## COMMENT

Enzymes, particularly, proteolytic ones, have occupied a position of prominence in all theories devised to try to explain the phenomena of

anaphylactic shock. More recently, it has been assumed that histamine, preformed, exists in cells, and is bound by a peptide linkage to an amino acid chain of tissue proteins. Roche e Silva<sup>10</sup> suggests that peptones and antigens may act indirectly and activate intracellular enzymes (cathepsins) which release histamine, and that substances like trypsin and snake venoms may act directly to split the peptide bond and release histamine. Feldberg suggests the possibility of peptone formation as an additional factor, and in the case of snake venoms also a lytic substance known as lysocithin.

If we consider all the animals in Groups I through VI as a whole, crotalin seems to have had a significant effect in the prevention of fatal anaphylaxis. Since snake venom injected into guinea pigs liberates histamine (whether directly or indirectly, or both), it is convenient to rationalize that the small doses of crotalin used in Groups I through V in this experiment were effective through their ability to cause a release of histamine, and that a release of this substance over a period of days developed a tolerance to the drug in the animals. This presumed effect was more than 60 per cent effective in preventing fatal anaphylaxis. This would tie in with the work of Farmer<sup>3</sup> and others that pretreatment of guinea pigs with histamine protects them against anaphylactic shock<sup>2,6</sup> through a tolerance developed to histamine. The same rationalization would explain the anticipated failure in Group VII to prevent fatal anaphylaxis. In this group, in which the animals were treated with crotalin the day before the anaphylactic dose of antigen was given, there was insufficient time for the animals to develop a tolerance to any histamine released. The favorable results in Group VI, to be consistent with the theory advanced, must be explained on the basis of a single dose of histamine or histamine-releasing substance (crotalin), injected into an animal, being capable of developing in that animal a tolerance to histamine, if sufficient time is allowed to elapse. It is possible in the present instance, that the large dose of crotalin effected a slow release of histamine over a period of days. However, such speculations are beyond the scope of this paper.

Essex and Horton<sup>2</sup> feel that the so-called histamine tolerance may really be a release of epinephrine from enlarged adrenals which takes place after pretreatment of a guinea pig with histamine. Snake venom treatment produces the same effect on the adrenals.

The fact that nearly all the surviving animals had some of the symptoms of anaphylaxis, would appear to demonstrate that crotalin does not act by preventing sensitization, nor by preventing the union of antigen and antibody. It does not appear to be an anti-histaminic drug in the sense that benadryl is.

#### SUMMARY

Crotalin injected intra-abdominally, as pretreatment in sensitized guinea pigs, prevented fatal anaphylaxis in 63.1 per cent of the animals. When

crotalin was given as a single dose on the day before the shocking dose of antigen, crotalin did not prevent fatal anaphylaxis.

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### Sympathectomy As An Antiallergic Measure

(Continued from Page 101)

## SUMMARY

1. The antiallergic action of histamine injections was contrasted, in the same patients, with that of sympathectomy and the conclusion was drawn that the former is weak and nonspecific, whereas the latter was found to be absolute and selective.

2. A case is reported of stammering with tic and irritability ("problem-child") cured with conservative sympathectomy followed by elimination of pulse-accelerating allergens.

3. The antiallergic effect of a sympathetic ganglion block has been studied in one case (two tests), and it has been found to be of sufficient duration in this instance to permit a forecast of the probable antiallergic effect of sympathectomy.

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# Editorial

*The opinions expressed by the writers of editorials in the ANNALS are individual and do not necessarily represent the group opinion of the Board or of the College.*

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## THE ANNUAL MEETING

The third annual meeting of the College will be held at the Hotel Senator, Atlantic City, June 6-8, preceding the American Medical Association meeting.

Friday morning, June 6, will be devoted to registration and social informalities. This will be followed by an informal luncheon, after which there will be a scientific program. A wide variety of papers covering all phases of allergy will be presented Saturday morning and afternoon until four o'clock when there will be a general business meeting. Saturday evening there will be an informal dinner followed by the presidential address. The scientific program will continue Sunday morning and will end with a round-table discussion Sunday afternoon.

Dr. Gregory Shwartzman, Head of the Department of Bacteriology, Mount Sinai Hospital and Clinical Professor of Bacteriology at Columbia University will be the guest speaker.

A booklet containing the final program and other information will be mailed to all in ample time before the session. A brief mention of a few of the speakers and titles will be: Dr. Bram Rose, Montreal, "The Relation of the Histamine-Like Substances in the Blood to Allergic States;" Dr. Harry S. Bernton, Washington, D. C., "Paroxysmal Dyspnoea;" Dr. Harold A. Abramson, New York, New York, "Psychosomatic Medicine and the Allergic Patient (Round Table);" Dr. Julia Baker, Mexico City, "Allergy in Children as Related to Altitude;" Dr. Ethan A. Brown, Boston, Massachusetts, "The Use of Ethyl Alcohol Intravenously in Status Asthmaticus;" Dr. Maurice S. Segal and Dr. John F. Beaky, Boston, Massachusetts, "The Use of Isopropyl-Aminoethanol for the Management of Bronchial Asthma;" Dr. Nolan Kaltreider, Rochester, New York, "Pathologic Physiology of Emphysema;" Dr. George L. Waldbott et al., Detroit, "Adequate Diets in Advanced Chronic Asthma."

It is urged that every member of the College remain for the special session on allergy to be held by the AMA, Friday afternoon, June 13. This meeting is to be conducted by the Fellows of the AMA. There are now 700 members in the College who are Fellows in the AMA. It is our duty to have the largest national society in the world properly represented and co-operating in every way to make this session a success. In the event that a permanent Section on Allergy is established, there will be an executive session with election of officers in keeping with the procedure in all other Sections of the AMA.

Reservations, not including stayover for the AMA meeting, should be made direct through the hotels. After June 8, all reservations should be made through Dr. Robert A. Bradley, Convention Bureau, 16 Central Pier, Atlantic City.†

†See Pages 63 and 64, November 23, 1946, JAMA, for detailed information.

## SCOPE OF ORGANIZATIONAL ALLERGY

The founders of *ANNALS OF ALLERGY* realized at its very inception that our publication should include the widest scope of the entire field of allergy and immunology. *ANNALS OF ALLERGY* was therefore the first publication devoted to allergy which published and encouraged both theoretical and clinical papers in many phases of allergy, which inaugurated an editorial, which included a news item, and which provided a department of comprehensive reviews of the allergy literature and its sister sciences.

In keeping with this policy, the College was the first allergy society to encourage membership from the related sciences, such as plant pathologists, biologists, pathologists, entomologists, physiologists, dermatologists and otorhinologists to form a consulting staff. The attitude of the College was, and still is, that specialists in the various fields who constantly encounter allergy in their practice should be encouraged to qualify as specialists in allergy in their respective fields. Our belief, that it is a restricted view to have these specialists who have undergone the same discipline as internists and pediatricians subcertified by internal medicine and pediatrics, has been justified by the recent trend of events. The events, as described in our first paragraph, make it obvious that since the beginning of the College four years ago organizational allergy has taken a turn for the better.

From the start, the founders of *ANNALS OF ALLERGY* recognized deeply their responsibility in encouraging research in the entire gamut of diseases which might be connected with the allergic state. The importance of such research, both to the allergist's practice and to the growth of allergy itself, is now generally realized. It is encouraging to see, therefore, that the efforts of the founders of the College and of the *ANNALS* are bearing fruit outside their own organization.

### Antihistaminic Substances

(Continued from Page 125)

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# Department of Clinical Pathology and Laboratory Procedures

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## THE MANUFACTURE OF ALLERGENIC OIL EXTRACTS—LEDERLE METHOD

THE Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York, generously has turned over its process of manufacturing allergenic oil extracts to the American College of Allergists, for which the College is deeply appreciative. It has been the policy of the College to make public all procedures for extractions, as was done in the January-February issue of the *ANNALS* when reporting on the standardization of dust extract. The College is therefore pleased to present in this issue the manufacturer's method of preparing allergenic oil extracts so kindly furnished, that it may be available for the use of all allergists.

At the time of the deletion of the allergenic oils from the Lederle price list, the standard method used for their preparation was the one outlined below. This method was based mainly on the result of clinical reports from Dr. Marion B. Sulzberger in the treatment and diagnosis of contact dermatitis with allergenic ragweed oil. It superseded a former one in which the leaves were first extracted with acetone and diluted with toluol, which is described below. The substitution of toluol for acetone for the preliminary extraction minimized oxidation, was time-saving and economical, and yielded extracts which kept their activity unimpaired for more than five years instead of one year.

### METHOD OF PREPARATION

Green leaves are ground in toluol immediately after collection. The mixture is stirred with a vapor-proof mechanical mixer for one hour for more complete division of the leaves and to facilitate extraction. It is then allowed to stand for one week at room temperature in an airtight container. The supernatant toluol is decanted and filtered through a Seitz clarifying pad. Decantation is effected so there is no admixture of the supernatant toluol with the water phase which separated at the bottom of the container. The water phase is discarded.

The toluol filtrate is made 10 per cent charcoal (not vegetable charcoal) and shaken vigorously in a mechanical shaker for at least one half hour. From time to time small samples of the mixture are withdrawn, filtered, and the filtrate compared with a sample of the original clarified toluol extract (not charcoal treated) for color and clarity. The



charcoal treatment, beside eliminating gum and chlorophyll, etc., from the extract, removes also traces of  $H_2O$ . If the filtrate of the charcoal-treated extract shows the slightest trace of chlorophyll when a drop of it is allowed to evaporate on filter paper, or is not of a reddish brown color, the charcoal treatment should be repeated. For the second charcoal treatment from 2 to 5 per cent charcoal is usually sufficient. The charcoal used for absorption should not contain any trace of moisture. The charcoal-treated extract is then distilled under reduced pressure until the toluol concentration in the oily concentrate obtained upon distillation is about 30 per cent. This concentrate represents the stock bulk extract. This extract will usually remain active as long as the menstruum for the oily residue is toluol in not less than the stated proportion. Allergenic oils which have been stored in the above concentration in acetone as a solvent were not as active as the oils stored in toluol. The allergenic oils both for diagnosis and for treatment are prepared from this toluol-preserved stock extract.

For obtaining the diagnostic oils, the stock bulk extract is distilled under reduced pressure until toluol-free. The temperature of the water bath should not exceed 65 degrees Centigrade. The oily residue left after distilling off the toluol is made 50 per cent dry acetone and allowed to remain in a freezer at minus 2 degrees Centigrade for twelve hours in an air-tight container. To minimize air exposure of necessity connected with the addition of 50 per cent dry acetone to the residue, total solid is determined on the bulk toluol extract prior to distillation. The amount of acetone to be added to the residue from a given volume of the extract for a final concentration of 50 per cent acetone can easily be computed without too much manipulation or chances of oxidation of the active principle.

The small amount of flocculent precipitate which forms in the extract during refrigeration is separated by filtration through dry sterile Seitz filter under positive pressure. Nitrogen under pressure is used as a source of the positive pressure. The temperature of the refrigerator in which the filtration is carried out must not be higher than 10 degrees Centigrade. The total solid is again determined on the sterile acetone filtrate. The acetone content of this final residue is adjusted to 30 per cent. The final material is filled at once in glass capillary tubes, and the tubes sealed.

The allergenic oils used for treatment are made from the filtrate of the solution of the oil in cold acetone. Total solid is determined by weighing the residue obtained upon evaporation to a constant weight of 1 cubic centimeter of the acetone extract in a vacuum desiccator over calcium chloride. Then a measured volume of the cold acetone filtrate is made acetone-free by distillation under reduced pressure. To the residue left after distillation of the acetone, sterile almond oil is added so the final mixture represents a 5 per cent solution by weight of the acetone residue

in sterile almond oil. The weight of the oily residue is computed on the basis of the total solid content of the acetone extract. To each 100 cubic centimeters of the final almond oil mixture 10 cubic centimeters of dry acetone are added as preservative. With the usual aseptic precautions, this final mixture very seldom shows any contamination. It is tested for sterility and filled as soon as possible in 0.5 cubic centimeter ampules to prevent oxidation of the active principle and loss of acetone through evaporation.

Diagnostic vegetable oils should not contain less than 10 per cent acetone or more than 30 per cent. For animal oils, however, the acetone content necessary to keep them liquid may be as much as 50 per cent. Lederle diagnostic ragweed combined oil consisted of an equal part of the final acetone residue of high and low ragweed. The total solid of the mixture was 70 per cent with an acetone content of 30 per cent.

The oil used for treatment contained five parts of the final acetone solid in one hundred parts of almond oil with 10 per cent water-free acetone added as preservative. The use of sterile almond oil does away with the necessity of sterilization by Seitz filtration.

The allergenic oils of spices and primrose contain 0.5 per cent of the final acetone solid in almond oil.

When the primary extraction is made with dry acetone, remove most of the water by adding granular  $\text{CaCl}_2$  in slight excess, drawing off the nearly dry supernatant acetone extract.

Add 1 per cent of norite to the acetone extract, and after sufficient shaking discard the fluid, collecting the norite on a filter (avoid drying of the norite).

Transfer wet norite to toluol, shaking over night. In the case of poison ivy 20 to 30 such extractions with toluol yield worthwhile quantities of oleoresin, which may be pooled and filtered. An aliquot portion is evaporated, and the residue weighed. A quantity of vegetable oil equal to or twice the estimated total solids in the pooled extract is added to protect the excitant from oxidation, and the toluol is distilled off in vacuo (nose-test for complete removal).

Excepting Rhus, primrose and spices, 5 per cent extract has been found to be tolerated without unpleasant reaction. Rhus, et cetera must not be stronger than 0.5 per cent for injection. Turpentine in oil has been injected 0.1, 0.2, 0.5 and 1 per cent intramuscularly with good therapeutic results.

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# Progress in Allergy

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## MISCELLANEOUS ALLERGY

### A Critical Review of Recent Literature

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A review of the literature of miscellaneous allergy is a very inclusive undertaking. Rightfully, those subjects adequately covered in the other issues of the *ANNALS OF ALLERGY* have been eliminated from this survey. The inclusion of some articles and remarks that may be a repetition of previous reviews, or which should be included in such reviews, has been intentional in order to emphasize a point or to cover the subject from a different viewpoint.

For purposes of presentation and discussion, the material herein reviewed will be presented according to the following outline:

1. General.
2. Respiratory.
3. Dermatological.
4. Gastrointestinal.
5. Headache: migraine and Ménière's.
6. Periarthritis nodosa and agranulocytosis.
7. Infection.
8. Histamine and antihistamine.

#### GENERAL SURVEY

The majority of the papers published during the past year have given emphasis to problems of investigation or of therapeutics. Burrage<sup>18</sup> presents a plea for the use of common sense in the allergic diseases. He outlines four illustrative cases in which the history and physical findings were suggestive and diagnostic of an allergic background, but in whom mismanagement of therapy was based upon over-enthusiasm and optimism. In his opinion, the history of the present illness is the most important single feature of an allergy investigation. To base a therapeutic program and suggestions upon skin test findings alone is neither proper nor wise. The interpretation of the findings should be made with an eye on the history and not "with magnifying glass technique."

Feinberg<sup>45</sup> also stresses the importance of the history in diagnosis and in the proper management of the allergic patient. He classifies the skin test, by any method, as a useful tool to aid in the complete survey and one to be used as such in outlining future therapy. This author has reviewed some of the early and modern accomplishments in the field of this specialty. Chief among these has been the discovery of new allergenic agents. Others, which are interestingly discussed, are chemical hypersensitivity and a more thorough understanding of the anaphylaxis-allergy complex. He lists the histamine conception and the advances in its diagnostic and therapeutic use as a definite accomplishment of the past decade. The inclusion of obscure ailments—periarthritis nodosa, for example—in the allergic category is a real step in the proper direction. In this same paper, Feinberg discusses the features of this specialty which must be explained and thoroughly understood before adequate explanation of the allergic patient can be considered complete. The mystery of the allergic constitution has been one source of consideration to the

allergist, as has been the true mechanism of the allergic reaction. He wishes for more knowledge of the antigens that have been established and makes a plea for the continued search for new antigenic factors. An intensive study of nonspecific factors in allergy would involve work with those features so disturbing to so many patients and without explanation as to cause of principle—weather, variations in temperature and humidity.

In an effort at explanation of the marked influence of weather changes upon the allergic state, Petersen<sup>102</sup> has made use of a group of drug intoxications to illustrate the possibility that the changing tide of the organic state of the patient or the general population may play an important role in so conditioning the organism that clinical reactions may be established which seem to be allergic but which are not necessarily on a true allergic basis. A relative anoxia, dependent upon various agents, may play a definite role in the sensitivity of the tissue. He states that the chances for intoxication, as from a drug, are greater if the organism is relatively acid. In this condition, the membranes are more permeable, there is a trend to fatigue, and catabolism is increased while tissue turgor is decreased. Adequate buffering of this disturbance of acid-base balance as a factor in resistance is a necessity. The common conditioning factor in the biological swing between acid and base is the weather of the time. Sufficient alteration may occur to produce unequal distribution of any therapeutic agent, which occurrence may produce a variety of symptoms which need not be on such a true allergic basis as sensitization.

A comparison of scratch and inunction skin tests (with "Intraderm") has been reported by Herrmann.<sup>64</sup> These tests were done on sixty-seven cases of atopic dermatitis, comprising a total of 770 comparative tests. The inunction test was positive in every instance in which there was a positive reaction to the scratch test with the same allergen. Different skin sites produced differences in reactivity. Skin tests were most strongly positive in these areas immediately surrounding the affected skin. The same author<sup>65</sup> has experimented with allergen inunction with "Intraderm" in desensitization. Twenty-two patients using fifty-four allergens were employed. There was a remarkable reduction of reactivity in most instances after varying periods of application. Inunction and scratch tests became persistently negative with one-third of the employed allergens. Fewer than 4 per cent of the allergens failed to yield a significant reduction of reactivity. Clinical results showed fifteen of the twenty-two patients with distinct improvement or complete disappearance of their symptoms during the time of frequent allergen inunction. This work should merit further study with carefully controlled experiments in order that definite conclusions may be drawn.

Blood studies in the allergic patient have always been a source of interest to clinicians. The presence of a predominant eosinophilia is often indicative of an allergic condition but, in many instances, blood changes of this type point to tissues and areas other than those considered typically allergic. The significance of eosinophilia in malignant tumors has been discussed by Isaacson.<sup>73</sup> This author quotes the work of Kirk<sup>77</sup> in which the conditions responsible for an eosinophile count over 6 per cent have been listed. These include (1) allergic diseases of all types, (2) certain skin diseases, such as mycoses fungoides and pemphigus, and (3) parasitic infestations. Eosinophilia is also a finding in Hodgkins disease, periarteritis nodosa, Loeffler's syndrome, and scarlet fever. Isaacson stresses the presence of malignancy in the body as an important, previously omitted cause of eosinophilia. He reviews nineteen cases previously reported in the literature and adds fifteen instances of pronounced increase in eosinophile percentage. This eosinophilia, when associated with malignancy, is indicative of dissemination of the malignant process if other causes for the blood picture have been adequately explained. Evidence of this statement is given by the author in that 90 per cent of his patients presented evident metastases. A new technique for rapid accuracy of eosinophile counting

is offered by Discombe.<sup>34</sup> The dilution of one part of blood with twenty parts of the staining fluid, five volumes each of 1 per cent aqueous eosin Y and of acetone, and ninety volumes of distilled water, results in clear satisfactory smears. Using a Fuchs-Rosenthal counting chamber, a mild eosinophilia of 400 to 500 cells per cubic millimeter was demonstrated in quiescent asthmatic patients, as compared to the normal count of 0 to 240 cells per cubic millimeter. Alteration of the white cell membrane may result in increased fragility of these cells in transitory leukopenia as demonstrated by Squier.<sup>113</sup> He presents evidence to show that this increased fragility does not appear to be a result of any change in the relative proportions of the different white cells. Further studies of the blood in the allergic patient have convinced Randolph and Rawling<sup>101</sup> of the importance of the leukopenic index in uncontrolled clinical allergy with unknown food sensitivities. Accentuation of the evidence of sensitivity is obtained by determining the postdigestive leukopenic response in those patients in a state of clinical intolerance. This state is reached by previously including the suspected or tested food in the diet, eliminating it for four or five days prior to the test, and then resuming the trial use of the previously omitted food at the time of the count. They feel that there is a high degree of correlation between the presence of a post-ingestive leukopenia of 10 per cent or greater and the production of symptoms from food ingestion.

The use of the sedimentation rate as an aid in the diagnosis of allergic and non-allergic states has been suggested by Parsons.<sup>100</sup> A review of over 3,000 rates reveals that the proper use and interpretation of this laboratory aid may prevent the performance of unnecessary allergy investigative procedures in questionable cases. Infection and other conditions responsible for increased sedimentation rates may complicate the picture, but allergic diseases and syndromes show normal sedimentation rates. This procedure is not diagnostic, but is a definite aid in differentiating the infectious from the allergic patient. Fidler and Waters<sup>46</sup> have shown that in dog anaphylaxis the platelet count can be considered to be of value as an index of sensitivity in doubtful cases. Platelet changes were studied in shocked dogs within two to ten minutes after the injection of the antigen. A sharp fall in from 2 to 20 per cent was recorded. Peptone shocks paralleled anaphylactic shock in platelet response. Because heparin injection did not prevent the decreased platelet count, the authors felt that the resulting increased clotting time was definitely due to the decrease in the platelets in shock.

As Feinberg<sup>45</sup> has stated, the mystery of the allergic constitution is one of the features of this work that must be solved. The difference in response to drugs and similar agents lends emphasis to this suggestion. Gastineau and Leavitt<sup>50</sup> have reported their patient who developed generalized urticaria and edema due to insulin sensitivity. It was imperative that the insulin be continued because of the glycosuria. Benadryl, given orally, adequately controlled the urticaria, but the angioneurotic edema persisted. Eventual injection of the insulin with an equal amount of benadryl solution prevented local reactions but had no effect upon the generalized symptoms of sensitivity.

Delayed serum sickness due to penicillin sensitivity has been discussed by Gordon<sup>56</sup> and Eisenstadt.<sup>41</sup> The former author noted the onset of the symptoms of serum sickness two to seven days after the penicillin therapy had been discontinued. The duration of the typical symptoms was from seven to ten days and responded to no medication other than epinephrine. This reviewer recently had two patients, mother and daughter, who had been given oral penicillin in the treatment of an acute infectious respiratory process. Six days after the penicillin had been ceased, generalized severe urticaria was encountered. Both patients showed immediate relief with the use of pyribenzamine. It has seemed that the delayed type of reaction is almost more common than the immediate type of reaction with penicillin usage. State and Wangensteen<sup>114</sup> used intravenous procaine in the treatment of

delayed serum sickness. There were no unpleasant reactions in twenty-seven patients. The procaine was given in dosages of 1 gram in 500 c.c. saline over a period of two or three hours.

Liver sensitivity is presented in some patients with symptoms similar to those of foreign protein reaction. Schwartz and Legere<sup>100</sup> report sixty-eight instances of liver extract sensitivity in a total of 396 patients receiving treatment for pernicious anemia. Of these, nine patients obtained complete relief with a change in the brand of extract used. The authors advise this procedure as the most simple expedient and the one to be given first trial. A dosage reduction may give the desired freedom from reaction. Desensitization with the liver extract was also successful, but the use of a histamine-protein compound, resulting in the production of histamine antibodies, gave relief in ten of the eleven cases in which it was used and in which other methods had been unsuccessful. Englehardt and Baird<sup>42</sup> recommend the oral use of thiamin hydrochloride rather than the parenteral administration of the preparation. They recount their experience with a patient who had taken thiamine for six weeks, then after a two-month rest resumed injections. The reactions which he experienced were readily controlled by epinephrine. Using the same material, Reingold and Webb<sup>105</sup> report the following experience: Their patient had received three intravenous dosages of thiamin hydrochloride without reaction, but within ten minutes after the fourth, given in equal dosage, symptoms of a general reaction were shortly followed by exitus. Death from pontocaine hydrochloride has been reported by Ahroon.<sup>3</sup> His patient, in whom a 2 per cent solution of pontocaine was used before bronchoscopy, had no reaction. Ten days later, similar use of this drug resulted in general reaction and death. The suggestion is made that the death may have been due to the ten-day interval for sensitization or else that the drugs used for sedation may have been given in too small a dosage on the second occasion.

Approximately 80 per cent of 129 children susceptible to flea bites received benefit from the treatment with a polyvalent flea extract. Hatoff<sup>61</sup> used only four injections of the antigen and suggested that this method may be of use in control of some diseases of insect origin. Experimental anaphylactic shock in dogs was shown by Graña<sup>57</sup> to be chiefly involved with the function of the liver in that animal. It is the liver that is chiefly responsible for the liberation of heparin and the increase of blood histamine. He has also revealed that though the histamine is released from the intact liver during the shock, such an occurrence is not present if the isolated liver is perfused with the antigen.

Golz<sup>55</sup> assumes that angioneurotic edema and urticaria are the predominant manifestations of recurrent tertian malaria. In the present case report, he states that he considers the malaria parasite to be the allergenic excitant, with the skin as the shock organ. Grazier<sup>58</sup> reports a similar occurrence. His patient experienced urticaria with each malarial attack. This author states that, in 500 cases of malaria, he witnessed but one instance of specific sensitivity to the parasite. A local physician<sup>126</sup> reported to this reviewer his experience with a malaria patient who could predict the onset of parasitic symptoms by his asthmatic symptoms. The patient had no evidence of respiratory allergy other than that associated with malarial seizures.

Criep<sup>26</sup> has divided allergic arthropathies into five groups: bacterial allergy evidenced by prolonged chronic infectious arthritis; transient articular swellings resulting from administration of foreign protein or drugs; swellings in association with Henoch's purpura; intermittent hydroarthrosis; and intermittent swellings and joint pains which are frequently mistaken for subacute arthritis but with no evidence of infection. The history is an important part in the diagnostic plan. Food elimination was important in affording relief to four of Criep's patients. He states that the mechanism of the allergic arthropathies is the same as in urticaria and angioneurotic edema, with the synovial membrane replacing the skin as the affected shock tissue.

## PROGRESS IN ALLERGY

### RESPIRATORY ALLERGY

Nomenclature can be misleading and in this respect Zonis<sup>130</sup> presents his ideas for clarification. He suggests that the suffix "itis" be added and the descriptive adjective allergy be used when applied to allergic respiratory disease. In this way, allergic rhinitis would as adequately explain the condition as would asthmatic bronchitis.

Walton and Dudley<sup>131</sup> have completed a very comprehensive survey of the mold content of the air in Manitoba. Over a period of six years they have found that the airborne fungus spores in that Canadian area are similar to those reports in the United States. *Alternaria*, *hormodendrum*, yeast, monilia and rusts were found to be present in the greatest and most significant amounts.

Postnasal drip has been given as the result of many abnormal states, and Proetz<sup>103</sup> feels that many of these complaints may be answered in modern living conditions. Central heating systems, thermal changes, fungi, allergens (inhaled or ingested), dusts, bacteria, and excessive or prolonged medication are a few of the responsible factors. He recommended that therapy be directed at the cause rather than at the sinuses.

The deleterious effects of the prolonged use of vasoconstricting agents for the relief of nasal obstruction are discussed by Lake.<sup>79</sup> Many patients present the results of the abuse of nasal tissues with nose drops. He terms these conditions as "rhinitis medicamentosa" and finds that prolonged treatment of this type produces congestion of the turbinates and gives to the mucous membrane a pale, boggy and allergic appearance. Treatment consists of the cessation of topical medication and the institution of other specific or nonspecific measures for relief.

Barach, et al.<sup>11</sup> state that the physiologic basis for the use of penicillin aerosol and negative pressure in sinusitis is as follows: A negative pressure of approximately 60 mm. Hg is intermittently produced in the sinuses during the inhalation of a fine mist of penicillin. Air withdrawn from the sinuses during the suction cycle is replaced by penicillin aerosol when the pressure in the nose becomes positive. Aeration and drainage of the paranasal cavities, and the deposition of penicillin on the mucous membrane, follow this procedure unless the orifices to the sinuses are completely obstructed. In 122 courses of therapy in 110 patients, marked improvement occurred in thirty-nine, moderate in forty-three, slight in seventeen, and no improvement in twenty-three. Significant x-ray changes were demonstrable after therapy. A change was also evident in the comparative cultures of the nasal or sputum discharges.

Freedom from nasal symptoms of vasomotor rhinitis is reported in 67 per cent of patients by Renander.<sup>106</sup> This author used roentgen ray therapy in 226 cases of vasomotor rhinitis with the above beneficial results. Relief continued for over one year in half of those treated. Treatment consisted of three exposures over the nose and sinuses at one-day to two-day intervals with a minimum effective dosage being determined as 100 to 150 roentgen units.

The essential differences between dyspnea and shortness of breath are the background for an enlightening editorial.<sup>38</sup> A perusal of the literature shows that many authors unjustifiably use these terms interchangeably. Dyspnea connotes a sense of choking or throttling, and is almost invariably a symptom of coronary artery disease or of left ventricular failure. Dyspnea is also descriptive of the respiratory difficulty of asthma or of bronchial obstruction. Shortness of breath simply means air hunger due to oxygen want. Myocardial insufficiency causes shortness of breath, but simple air hunger may be a normal occurrence and has no definitive connotation. Bronchial asthma is a source of dyspnea. The relief of this complaint rests in many fields according to the inclination of the physician in charge. Godlowski<sup>51</sup> has used insulin shock as a means of obtaining relief in his patients. It seems to operate, according to this author, by means of a stimulus to the adrenal medulla,

inducing a hyperproduction and dissipation of adrenalin. In eight patients with allergic bronchial asthma, seven responded with complete relief for as long as eight to thirty months.

Henderson<sup>63</sup> feels that psychogenic factors act as "trigger mechanisms" through suggestion. It is his opinion that the attack may also occur as a type of conditioned reflex, with the attack originally a reaction to some allergic substance, but that other stimuli may become conditioned to precipitate attacks.

Lumbar puncture with the removal of a few milliliters of spinal fluid resulted in improvement in eight patients with severe bronchial asthma. Jonuleit<sup>74</sup> reintroduces this form of therapy, the mechanism of which is considered unknown.

Hobeeb<sup>67</sup> presents the opinion that silica is a substance that is appreciably soluble and is not inert. Upon contact with the body fluids, some silica is converted to a highly toxic, highly active colloidal silica which as an end-product can cause bronchospasm. The fact that epinephrine will give temporary relief in silicosis is the basis for the belief that there is bronchospasm present. Further evidence of the allergenic effect of silica is furnished when histamine causes dyspnea and wheezing in silicotic patients. Many of these patients will show an eosinophilia.

Pulmonary infectious processes have instigated several interesting reports. Penicillin aerosol in the treatment of bronchiectasis has met with encouraging results. Levine<sup>81</sup> feels that medical treatment of bronchiectasis is a necessity, for surgical lobectomy is possible only if the lesions are localized and surgical removal is possible and indicated. He feels that chemotherapy is not productive of results worthy of prolonged use. Nehil,<sup>93</sup> on the other hand, is of the impression that lobectomy is the only real cure for the bronchiectatic lung. Bobrowitz<sup>15</sup> and his associates have reported the use of penicillin by various methods of administration. They had twelve patients in whom penicillin was used from four to 115 days in a dosage of from 500,000 to five million units. They found the highest concentration of sputum penicillin to be obtained by the intratracheal route of administration. Inhalation was less effective and intramuscular injection was least effective. Their results are reported as excellent. Abramson<sup>1</sup> determined that hydrogen peroxide solutions and penicillin in aerosol provide a method of approach to the destruction of both Gram-positive and Gram-negative organisms. He noted a decreased amount of cough and sputum with such aerosolization. Thomas<sup>116</sup> and his associates at the Cleveland Clinic reported that 48 per cent of 190 consecutive cases of bronchiectasis had a history of major allergy. Results were described as "dramatic" with the use of 7.5 grains of sulfadiazine orally four times daily for four weeks. In twenty-one cases, allergic management alone was productive of encouraging benefit. Additional measures used in all patients were the aids of postural drainage, rest, diet and high vitamin intake. The failure of penicillin aerosol in nine patients prompted the use of streptomycin aerosol with good success by Olsen.<sup>96</sup> The use of antibiotics by aerosol is suggested by the author as a preoperative measure or in some indicated instances as a temporary measure in nonsurgical cases.

Irwin<sup>72</sup> suggests a study be made for the presence of microfilariae in all cases of tropical eosinophilia. The two cases which he reports were admitted to Cushing General Hospital with a diagnosis of bronchial asthma, but investigation and observation failed to corroborate the diagnosis. Each patient had been well until in service in the southwest Pacific. Evacuation to this country and treatment with arsenicals produced improvement by the third injection. Arsenical therapy is also advised by Hunter<sup>71</sup> in the management of tropical eosinophilia. His patient showed an eosinophilia of 59 per cent on one occasion and 74 per cent on another. Leukocytosis returned to normal without any further asthmatic symptoms following the use of weekly arsenic therapy.

The pathology of Loeffler's syndrome has been presented by Baggenstoss, Bayley and Lindberg.<sup>10</sup> Their patient was originally seen in 1944 for observation to



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rule out tuberculosis. Physical examination was essentially normal. Roentgenograms revealed upper lobe shadows while the differential count showed a 35 per cent eosinophilia. At post mortem late in 1944, numerous irregular-shaped regions of increased density were found scattered throughout both lungs. The pleura was thickened over these lesions. Results of eventual tuberculosis investigation were negative. Replacement of the normal parenchyma of the lung by masses of fibroblasts and collagenous fibers was demonstrated on histologic examination. There was an abnormally large number of eosinophilic leukocytes. The most important and significant features of this case were the character of the bronchial lesions, the advanced organization of the pneumonic exudate, and the presence of vascular lesions.

Transitory pulmonary infiltration thought to be due to "pneumonid" is discussed by Eichwald and Singletary.<sup>40</sup> Their patient was one admitted for minor gynecological surgery and in whom an eosinophilia and transitory lung lesions were determined. The lung lesions were thought to be a secondary allergic response to a low-grade chronic infection of the cervix and endometrium. The familial aspect of this condition is stressed by Blanton.<sup>14</sup> In presenting and reviewing four cases he has used the pulmonary clearing following adrenalin administration as a diagnostic point. This author believes that Loeffler's syndrome is due to the allergic response to various allergens. That "allergic background" can prepare a patient for eosinophilic pneumonitis has been postulated by Spector<sup>112</sup> in his presentation of a patient who developed bronchial asthma after having had an attack of transitory pulmonary lesions in apparent association with nasal polyps.

The Council on Pharmacy and Chemistry of the AMA has reported that the product ethylene disulphonate is indistinguishable from distilled water. They state that this material is without therapeutic value, and could not substantiate the claim of solution concentration.<sup>107</sup>

### ✓DERMATOLOGICAL ALLERGY

The modern treatment of acne has been discussed by Warren,<sup>125</sup> who deals chiefly with the local therapy. She states that acne vulgaris is the most common skin disorder of adolescence. Association of the skin lesions with general metabolic and endocrine changes as well as with disturbances of the sweat glands and sebum is stressed. The use of thyroid extract in small doses, in combination with local therapy and general skin cleanliness, is recommended. Astringent lotions of copper sulfate or calamine with ichthyol are advised if a drying effect is desired. Dietary management with elimination of known or suspected affecting substances often leads to surprising results.<sup>133</sup> Relief within a six-week period has been reported with dietary guidance in such dermatologic complaints as acne, eczema, psoriasis and urticaria. Turnbull<sup>121</sup> feels that a correct diet plan is all-important in these conditions of skin involvement. This reviewer is in agreement with the dietary management of those indicated lesions, with the exception that good results are hardly to be anticipated in placing psoriasis upon a food allergy basis. Turnbull, however, has included in his thirty case reports, instances of severe psoriasis that have responded very well to good elimination.

The term "allergic neurodermatitis" has been offered by Bernstein<sup>12</sup> in application to those instances of skin involvement that are not truly allergic nor truly neurotic. In reporting six cases, he outlines the chief symptoms as pruritis, vesiculation, erythema, edema and exudation. For good results therapy must be directed at both the allergic and the neurotic aspects of the condition.

The influence of military medicine can still be seen in the patients being studied at this date following the end of hostilities. Various lesions from the use of atabrine have been reported. Nelson<sup>94</sup> and Whitehill<sup>128</sup> describe their patients who presented skin lesions due to the oral use and the handling of atabrine. In each instance, a positive patch test was obtained with the suspected material. More

serious involvement of the cornea with edema has been found by Chamberlain and Bales<sup>21</sup> to be due to quinacrine (atabrine) sensitivity. They had four cases in whom visual impairment was the initial complaint. These patients had been on protective dosages of quinacrine for a period of four to six weeks. All tests were negative, but withdrawal of the drug produced relief and a return to normal vision. These authors have suggested that the hepatic function in atabrine-sensitive patients should be investigated before the patient has been discharged. That there is a definite incubation period between the beginning of atabrine administration and the onset of the drug eruption has been emphasized by Kierland.<sup>76</sup> He describes forty-nine patients whose cutaneous lesions were morphologically similar to lichen planus. The local manifestations of this eruption are far more pronounced than in the usual case of lichen planus. The course is prolonged, regression is slow, and convalescence often requires many months. Treatment of any type has been unsatisfactory, but immediate and continued withdrawal of the causative drug is imperative. Atabrine sensitivity has been the causative factor in fatal exfoliative dermatitis and hepatitis. Agress<sup>2</sup> reports fatalities in three of five Chinese patients. Jaundice and other evidence of hepatitis—elevated temperature, leukocytosis—appeared several days after the onset of the initial rash. Four of these five patients responded with positive tests by patch with atabrine. Treatment consists of the immediate removal of the drug, accompanied by measures to combat the progressive hepatic lesions.

Sensitivity to the active principle of penicillin was found to be the cause of contact dermatitis in three of four patients studied by Friedlaender and Feinberg.<sup>47</sup> They could determine no relationship between the contact dermatitis due to penicillin and symptoms arising from clinical mold allergy. Other types of dermatologic response to penicillin have been observed. Elevation of temperature and a definite increase in the pulse rate noticed two to five days after the discontinuation of the therapy have been reported by Macy and Harp.<sup>85</sup> These initial warning signals were followed by a serum sickness type of reaction evidenced by facial edema and generalized urticaria. They feel that the deviation of the temperature curve and the elevation of the pulse rate are important points to be noted in the after-care of penicillin therapy. An increase in the severity of urticarial lesions as a result of penicillin sensitivity was noted with each successive therapeutic dosage by Zeller.<sup>135</sup> Complete clearing was noted five days after the drug was eliminated from the schedule. Very small dosages of 50 units were able to produce lesions while the patient was in the reactive stage, but later comparatively large amounts caused no complaints. The same indications and essential findings were determined in regard to the testing for such sensitivity. It is entirely possible that some of the reactions to penicillin are due to sensitivity to the pure drug itself rather than to the impurities. Such is the feeling of Nolan and Pedigo<sup>95</sup> who investigated this point in reporting their patient with an exfoliative dermatitis while under penicillin therapy. The original patch test was positive but subsequent tests, using different batches and brands of the drug were negative. They assumed from this, that their patient's discomfort and complaints arose from a sensitivity to some impurity in the material rather than from a true drug sensitivity.

Service<sup>110</sup> reported the use of intravenous nicotinic acid in the treatment of urticaria due to penicillin sensitivity. The dosage advised was 35 milligrams in 10 c.c. of distilled water. The usual aids—epinephrine, ephedrine, calcium, vitamin K, and morphine—were not entirely satisfactory in this physician's hands. He therefore tried nicotinic acid in the indicated dosage, and in forty-one instances found a second injection to be necessary on only four occasions. The relief with this medication was said to be prompt, lasting and satisfactory.

Anthallan in dermatology was found to be a safe, able and worth-while drug by Ereaux and Craig.<sup>44</sup> They found it most useful in pruritis, and it was not as-

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sociated with unpleasant side effects. Inasmuch as anthallan is a weak antihistaminic drug, it was their recommendation that the medication should be given after meals. As an antipruritic agent, however, Epstein<sup>43</sup> was able to use theophylline ethylenediamine with exceptionally good results. In a dosage of 7.5 grains in 20 c.c. of fluid, the intravenous administration resulted in immediate relief in twenty-five patients with severe itching due to various causes. The average duration of relief was four hours, but the medication was not repeated more often than once in twenty-four hours.

### GASTROINTESTINAL ALLERGY

Eosinophilia is not necessarily a diagnostic point in differentiating the allergic from the nonallergic patient. Page<sup>90</sup> states that a predominance of eosinophiles is of value on his gastrointestinal service only in the diagnosis of hookworm disease. In four patients with the syndrome of eosinophilia, leukocytosis and gastrointestinal complaints, complete case reports seem to substantiate this view. He has reported 1,353 patients admitted to his wards. Nine per cent of these showed an eosinophilia of 5 per cent or more in their circulating blood. In acute gastroenteritis an eosinophilia of 22.7 per cent was usual. In twenty-two of 192 duodenal ulcer patients, the eosinophilia averaged 7.3 per cent. With these somewhat misleading figures, this author felt that the blood finding could not be reliable except for the suggestion of further search for the hookworm parasite.

In a well-controlled experiment, Demuro and Ficori<sup>32</sup> determined that there were two stages to an allergic reaction in the gall bladder. These phases were listed as the degenerative-exudative stage and the proliferative period. Their findings were based upon their examination of twenty rabbits which had been sensitized by four intravenous dosages of 2 to 3 c.c. of sheep serum. The exciting dose was given directly into the gall-bladder cavity.

As a result of food sensitivity, some patients may have "violent storms" which seem to go through the autonomic nervous system, producing symptoms described as alarming. Alvarez<sup>4</sup> reports the instance of a female patient complaining of prostrating attacks at intervals of every two to three weeks. Tachycardia, anxiety, weakness, dyspnea, and a profuse vaginal discharge were the outstanding complaints. Complete avoidance of milk and milk products permitted relief and freedom from the recurring attacks. In explanation of the delayed response to ingested food by an allergic patient, Blamoutier<sup>13</sup> presents a patient who reacted positively to material resulting from the simultaneous incubation of the allergens with gastric and duodenal juices. Previously, negative reactions had been determined to the allergen (lamb) in the raw state. He assumes that the evidence substantiates the sensitivity to be due to a decomposition product of the food protein.

Careful attention to the dietary habits as revealed by an accurate history is of the utmost importance in giving relief to many patients with pruritis ani. Rugeley<sup>108</sup> has reviewed fourteen patients with such complaints that have been under his care. Elimination diets, food diaries, and trial and error investigation are used in close association with the results of allergic surveys. He feels that latent reactions are of greater significance than early reactions. Investigation of the allergic possibilities is recommended in pruritis ani before radical procedures are undertaken. Experiments which are of value in explaining the existence of positive skin and clinical reactions to substances which the patient has never eaten are reported by Tuft and Blumstein.<sup>120</sup> They investigated the existence and relationship of the various types of antigens existing in the fish family. By direct and indirect testing with six patients, they were able to determine the existence of a common antigen among the members of the fish family. The distribution of these antigens paralleled closely the zoological classification of the fish. Three fish-sensitive patients were exposed to the odors of uncooked fish with subsequent urticaria and asthma ap-

pearing in these patients within five to thirty minutes. Earlier appearance of symptoms was noted upon exposure of these patients to an atmosphere containing rather heavy fish odor emanations coming from kitchens in which fish were being cooked. Thus evidence is offered of the ability of fish odors to induce clinical symptoms in sensitive patients.

### HEADACHES

There are two schools of thought concerning the physiology of migraine. On the one side are those physicians who feel that the syndrome is divisible into two stages: the first is one of vasodilation, and the second is vasoconstriction. On the other side are those with the impression that the complaints arise primarily from vasospasm, with secondary dilatation producing the headache. With such a controversy over the physiologic aspect, it is understandable why the therapeutic measures would be divergent. Several papers published during the last year have dealt with the therapeutic problem of new drugs, new methods and new ideas. Alvarez<sup>5</sup> has written that "it is a waste of time to search for the cause in the digestive tract." He implies that the condition is one based entirely on heredity with the essential feature being a tense, nervous temperament. The opinion that this is a metabolic disorder, which can be diagnosed by the salt tolerance test and a demonstration of retention, has been offered by Goldzieher.<sup>53</sup> In reporting 100 cases, this author finds that the migraine patient responds well to a diet of high protein with special restriction of salt, water and carbohydrate intake. To this restricted program he adds organic potassium salts. The difference between "true" migraine and ciliary headaches is the subject discussed by Harris.<sup>60</sup> He feels that, though they are both "curable by alcohol Gasserian injection," the ciliary type of headache is characterized primarily by marked ocular congestion and lacrimation, two features which are notably absent from the history and findings of migraine. In this same vein, somewhat, Davis and Bick<sup>30</sup> lament the designation of any severe headache as "migraine." In their patients, consisting of flying personnel in the Army Air Forces, the term led to unpleasant relationships and occurrences. They feel that the designation of "migraine" should not be made without the rather definite diagnostic points. A history of severe, unilateral headache, associated with visual disturbances, nausea and vomiting, was considered of importance. Crowe<sup>27</sup> studied his 100 patients from the standpoint of allergy, endocrinology and physiology. Only one patient showed glandular hypofunction. Complete allergy investigations were done on these patients with particular reference being paid to the dietary and gastrointestinal factors. Skin-test findings were not considered salient, however, unless at least ten or more strong reactions were obtained. The principle sensitivities determined by Crowe were wheat, legumes, seafoods and milk. He reports that all patients remained entirely free of migraine as long as strict dietary measures were followed and as long as the emotional factor was controlled. No other such optimistic outlook has been uncovered in this review of the subject.

Thomas and Butler<sup>117</sup> have reviewed the use of histamine in the treatment of migraine. Since histamine is lacking in essential molecular structure these authors feel that it could not produce an allergic state. In their opinion, histamine sensitization is really a lowered tolerance for the material. The success of therapy with histamine depends upon increasing this tolerance or upon the increased production of histaminase. Treatment, according to this theory, consists of the injection of 1 mg. histamine acid phosphate diluted in 500 c.c. of physiologic salt solution. Six injections are given on successive days. Early in the schedule, the rate is maintained at 5 drops per minute with an increase or decrease dependent upon the individual response. A decided drop in blood pressure, facial flushing, tachycardia or appearance of headache symptoms are indications for immediate slowing or

withdrawal of the medication. In seventy-five patients, thirty were found to obtain complete relief, eleven experienced temporary absence of symptoms with eventual complete relief, twenty-five with partial relief, and only nine were not benefited. These same authors later reported<sup>118</sup> the results of this same therapy in a total of 104 patients, of whom seventeen were male and eighty-seven were female. In this group, there were four responses to the medications; immediate relief, which was experienced by forty-two patients; immediate relief with eventual recurrence was seen by sixteen; gradual relief was noted in thirty-four, and no relief was obtained in twelve instances. Intravenous histamine should not be given to patients with peptic ulcer, vascular disease, or central nervous system disease.

Vitamin administration has been beneficially used by Goldzieher and Popkin.<sup>54</sup> They recommend the intravenous use of 100 mg. of sodium nicotinate, and report seventy-five patients obtaining complete relief. These headaches were of various types. The nine migraine cases studied were included in those seventy-five patients benefited, and the relief was present within two minutes following administration of the preparation. The degree of peripheral flushing was used as an indication of the expected relief. Riboflavin has been used in the treatment of migraine by Smith.<sup>111</sup>

Experimentally, dihydroergotamine (DHE 45) is eight to ten times less toxic in the cat and the dog than is ergotamine tartrate. Though their sympathetico-paralytic action is similar, they differ in that DHE 45 possesses no uterine effect as does ergotamine tartrate. Horton, Peters and Blumenthal<sup>60</sup> employed this drug in 120 patients with migraine. Seventy-nine of these patients exhibited all the typical features of the diagnosis. Of these, 75 per cent experienced good to excellent results. The remaining forty-one patients with atypical migraine received good to excellent results in only 36 per cent. This drug will not prevent the future attacks, but immediate relief can be expected. The above authors noted toxic reactions to be definitely less (by three times) with the use of DHE 45 as compared to the use of ergotamine. The recommended dosage is 1 to 2 c.c. subcutaneously, intravenously, or intramuscularly, with repetition of the dosage in one hour if necessary. One c.c. contains 1 mg of dihydroergotamine methanesulfonate. No clinical change was noted in the blood pressure of the above patients. Clein<sup>24</sup> treated a series of twenty-eight patients with DHE 45. Sixteen of these were definitely allergic in origin, while the other twelve were classified as of unknown etiology. In the latter group, only three were relieved by the drug. Of the allergic group, eleven patients noted immediate (two- to three-hour) relief, which was quicker than that produced with any other previous medication. The absence of any side-effects was quite outstanding, in that only one patient felt nauseated and "jittery" with the injection but voluntarily returned for the same medication for subsequent attacks. Clein suggests that headaches not responding to DHE 45 should be those most amenable to histamine desensitization.

Marin<sup>86</sup> has used theophyllin (3 gr.) intravenously for the relief of migraine. Seven of ten patients experienced no recurrence, while three others obtained immediate relief by the same manner for subsequent attacks. These patients were also maintained on a daily oral dosage of nine grains.

Histaminic cephalalgia must be differentiated from migraine. The form of treatment is dependent on the diagnosis established. Walker<sup>123</sup> tries to reach a dosage of histamine of 0.6 c.c. in extending his patients relief. In his case report, he considers the symptoms as an alarm syndrome. Friedman et al.<sup>40</sup> feel that the experimental headache due to histamine injection results from a secondary rise in blood pressure. Twelve of fifteen patients stated that the headache thus produced was identical to the usual complaints for which they were seeking relief.

The pathologic picture in Ménière's disease is that of extracellular edema.

That the condition is not allergic in origin is proposed by Lindsay<sup>82</sup> who has had difficulty in securing evidence of an immunologic reaction in these patients. He feels that the condition is one of several inner ear diseases and that the etiology is very indefinite. However, all forms of medical treatment that have been successful in relieving the symptoms have been based on the concept that Ménière's disease is a form of allergy. The use of nicotinic acid as a vasodilator is described by Williams<sup>130</sup> as the "easiest of the vasodilators to administer." This preparation or histamine, in this author's opinion, is superior to the control of water and electrolyte metabolism but he suggests that all these forms of medical therapy be combined for best results. He uses nicotinic acid hypodermically, starting with a dosage of 25 mg. and increasing by this amount with each injection until a dose relieving symptoms, the so-called optimal dose, is reached. This has usually been 100 mg. depending upon the tolerance of the patient. This form of therapy should not be continued for longer than six months without a rest period of several weeks to a month. Epinephrine, atropine and benadryl are recommended for the relief of the acute attacks.

Some cases of Ménière's disease are ineffective in their response to medical therapy. Day<sup>31</sup> reports very good results in nineteen consecutive cases with labyrinth surgery. Fenestration of the labyrinth with destruction of the membranous labyrinth is described. Atkinson<sup>7</sup> feels that surgery should be attempted only as a last resort. He has reported his results with medical treatment as productive of relief in 80 to 90 per cent of the patients under his care. This same author in another publication<sup>8</sup> produces evidence to establish the validity of the intradermal histamine test, as a guide to therapy. Williams<sup>129</sup> found that in 122 of 362 cases, two or more of the following syndromes were associated: vasomotor rhinitis, vasodilating pain, myalgia, and endolymphatic hydrops. He therefore feels that all four can be conveniently included in the syndrome as physical allergy of the head.

#### PERIARTERITIS NODOSA AND AGRANULOCYTOSIS

Within recent years the association between some vascular lesions and the existence of an allergic state has been the subject of many interesting publications. This has been of particular concern to Harkavy.<sup>59</sup> Sensitization by foods, pollens, sera, drugs and bacteria may be followed by various degrees of hypergic reactions in the cardiovascular system. During the early, acute stages, these pathologic lesions can be reversible with the removal or the correction of the offending agent. The clinical course of these lesions is dependent upon the degree of involvement in the heart and the kidneys. Irreversible reactions in either of these organs will lead to fatal cardiac or renal failure as exemplified by seven of the sixteen patients studied. Such vascular lesions may be seen in any organ or system. Almost every writer mentions the reversibility and irreversibility of the lesions of periarteritis nodosa. Searching for possible causes, Bueser and Gardner<sup>17</sup> stress the lack of knowledge of known etiologic factors but suggest that the condition may be due to a virus. In their cases, one of the most consistent findings was an eosinophilia varying from 19 to 36 per cent. The duration of the disease is short, with fatalities usually occurring within one year after the onset of symptoms. Symptoms may be multiple and widespread, depending upon the degree and extent of involvement.

Moschowitz<sup>92</sup> states that the clinical aspects of periarteritis nodosa are the resultant of three large clinical backgrounds: rheumatic fever, glomerulonephritis and malignant hypertension, plus the consequences of the widespread lesions, affecting the circulation and the function of many organs. This disease is not one of senility, but may occur at any age. Vascular lesions in infancy, somewhat more rare than in later life, are not too frequently observed.

Wilmer<sup>132</sup> could find only two previous case reports in which the lesions were

discovered under the age of one year. To these, he adds two patients, one of whom died at the age of five weeks, and the second at the age of ten days. His first patient presented clinical symptoms at the age of four weeks. Vomiting, dyspnea, pallor, and leukocytosis persisted for seven days, and the diagnosis was made at the autopsy, revealing the right adrenal gland to be involved in an inflammatory mass. The second patient presented vomiting, abdominal pain, edema, purpura, fever and leukocytosis with an umbilical infection. He felt that the original infectious process may have had its origin in utero. Perilman<sup>101</sup> is of the opinion that anaphylaxis as a cause of the vascular lesions cannot be overlooked and that this theory is worthy of further investigation.

Higgins<sup>66</sup> reports his findings in six cases, all of which have some manifestations in common. He found that the organs most commonly affected were the kidneys in 80 per cent, the heart in 70 per cent, liver in 65 per cent, muscles in 30 per cent, and central nervous system in 8 per cent. Biopsy has not been of particular value in the clinical diagnosis because of the possible absence of typical pathological lesions from the sections that are made. The best results from this diagnostic source have been found in the examination of sections taken from purpuric lesions or from vascular nodules. Because of the variety of symptoms, this author feels that a diagnosis of periarteritis nodosa should be considered in every patient with obscure generalized symptoms.

One of five cases in the literature that have been diagnosed upon the evidence of retinal artery pathology has been published by Goldsmith.<sup>52</sup> He found an aneurysmal dilatation of the inferior temporal artery on examination of the fundus in a patient who had had a rather prolonged course of sulfonamide therapy. The administration of sulfonamides and sera increases the possibility of inducing hyperergic states. A personal history of allergy was absent in all eleven patients reviewed by Logue and Mullins.<sup>84</sup> Hypertension was present at some time or other in each patient during the course of the illness. Eosinophilia, however, was not a consistent finding and the suggestion was made that repeated examination was necessary in order to determine the true presence, which might vary with the activity of the disease stages. They offer the suggestions that the etiology of this affliction will be found in sensitization to sera, drugs and infection.

A definite etiologic agent was not proven in any of the seven patients reported by Diaz-Rivera and Miller.<sup>33</sup> Allergy was suggested in three patients because of the eosinophilia and migraine in one patient, and in two others because of appearance of a rash during their illnesses. The very acute, rapid onset and the short duration of the illness of their patients emphasizes the fulminating character of the condition. Illustrative case reports reveal the possibility that cerebral periarteritis nodosa may be curable as evidenced by one patient who recovered after surgical operation. Due to the protean clinical manifestations mistakes in diagnosis are common. The signs and symptoms have been divided into six large groups by these authors: cerebral, neuromuscular, cardiac, cutaneous, gastrointestinal and pulmonary.

It is the consensus of most writers that penicillin administration is of extreme value in combating infectious complications subsequent to agranulocytosis. Sulfonamide sensitization has produced fatalities in this connection. Cameron and Edge<sup>19</sup> recommend penicillin until the marrow has had an opportunity to recover. Their patient had received only 14 grams in a two-day period in an effort to combat a tonsil infection. Marpharsen therapy of syphilis is not without similar danger. McManus<sup>91</sup> had two patients in which penicillin permitted recovery from agranulocytosis due to this drug. One of these patients had a coexistent toxic hepatitis, and the antibiotic therapy proved beneficial for both the original infection and for combating the subsequent complication.

In recent months, the frequent use of thiouracil has shown that this drug is

not without its side-effects. Hendon<sup>62</sup> reports a patient who had received thiouracil for a period of several weeks before the cellular change was noted. Penicillin was then used to prevent intercurrent infection until recovery was possible. Five of a series of sixty-two patients are presented in detail by Lesses and Gargil.<sup>80</sup> These were treated with thiouracil for thyrotoxicosis. The agranulocytosis is thought to result from a bone marrow depression or a destruction of the leukocytes beyond the promyelocytic stage. The hypersensitivity to the drug, the dosage and duration of administration may all enter into the appearance of the blood disturbance. Re-administration of the drug in small doses after a reaction did not usually produce a second neutropenic response. The authors felt that this was due to desensitization.

#### INFECTIONS

The significance of a positive tuberculin test has been a source of much debate. The relationship of the positive tuberculin test to the presence of active infection has always been a puzzling problem. Clarke<sup>23</sup> has drawn the following conclusions concerning the degree of tuberculin sensitivity: (1) there is no relationship between the stages of the disease and the degree of tuberculin sensitivity; (2) there is a tendency for tuberculin sensitivity to be lower in patients with long histories and active pulmonary tuberculosis than in patients with short histories and active tuberculosis; (3) the presence or recent presence of pleurisy with effusion appears to lower the degree of tuberculin sensitivity; (4) there is a lower degree of tuberculin sensitivity with an inactive lesion than with an active one; (5) tuberculin testing may aid in the diagnosis of the minimal lesion.

Children under three years of age were classified by Edwards and Hardy<sup>39</sup> according to their response to various dilutions of old tuberculin. Over a period of years, those showing positive tests to 1 mg. of O.T. did not develop tuberculosis. Those giving a positive skin test reaction to 0.1 mg. O.T. included six with tuberculous infections. Twenty-two of 147 children reacting to 0.01 mg. O.T. died of tuberculosis within the years of observation and re-testing. There has been much discussion concerning the comparative results of testing for tuberculin sensitivity by the Mantoux or the patch-test method. Holden<sup>68</sup> discusses the use of a potent purified powdered tuberculin which was incorporated in a transparent liquid solution stated to be nonirritating and nonallergizing. The results of this transcutaneous testing were comparable with those obtained in intracutaneous use of 0.0002 mg. of purified protein derivative.

No positive skin test reactions were recorded by Clarke and Gilmore<sup>22</sup> in testing individuals who had not resided in areas endemic for *Coccidioides*. Cutaneous test with 1:100 dilution of coccidioidin was employed. This type of reaction is similar to tuberculin hypersensitivity. Intracutaneous testing with 1:2,000 dilution of an extract of *Dirofilaria immitis* revealed that a positive reaction could be considered as indicative of infestation. Zarrow and Rifkin<sup>134</sup> discovered 91 per cent of infected patients showing a positive reaction to the extract. Augustine and Lherisson<sup>9</sup> question the diagnostic significance of the test, however. They were unable to determine positive evidence of clinical manifestations of the disease in those who showed positive reactions.

A natural immunity to yellow fever vaccine has been described by Truit<sup>119</sup> in his case report of a patient presenting edema and urticaria following vaccine administration. This patient was not sensitive to egg on testing, but did present a markedly positive reaction to direct and indirect test with the vaccine. David et al.<sup>29</sup> produced very few minor constitutional symptoms in the intradermal administration of scarlet fever streptococcal toxin in rheumatic cardiac children. There were no findings of subsequent chorea, carditis nor arthritis.



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### HISTAMINE AND ANTIHISTAMINE

The action and counteraction of histamine have been the source of many interesting, instructive and controversial publications. Code<sup>25</sup> presents the action of histamine in a clear and comprehensible presentation. The effect of histamine upon smooth muscle is one of contraction, as seen in the bronchii, vascular system, intestinal tract and uterus. Upon the capillaries, the action of dilation and increased permeability is demonstrated in the skin and mucous membranes. As a secretagogue, the effect is noted in the lacrimal, nasal, pulmonary and digestive glands. Histamine plays a part in various pathological conditions and there are methods of controlling its effects. Dragstedt<sup>35</sup> lists the various methods of control application as follows: (1) Reduction of tissue stores, controllable since histamine in the tissues comes from the metabolism of histidine, an essential amino acid. There is no known way of augmenting the activity of histamine normally in the tissues. (2) Prevention of histamine release either by desensitization or hypsensitization. (3) Inactivation of released histamine which has proved unsuccessful. (4) Frustration of the effects of released histamine by the use of hapamine or similar material to make the tissues tolerant to histamine, by the employment of drugs such as epinephrine to counteract histamine, and by the use of specific antagonists.

The skin response to histamine is not reduced with treatment. Keeney<sup>75</sup> states that inasmuch as histamine is not an antigen, it is unlikely that the body forms antibodies to a substance so widely distributed. Attempts have been made to use a single histamine test as a screening outline for the identification of allergic states. Hulett<sup>70</sup> sought to bring this idea to the attention of the military authorities in an effort to identify readily the presence of allergy in inductees. He planned to use 0.05 c.c. of a 1:25,000 dilution of histamine in normal saline as a control. Reaction to this dilution would be considered as normal, with further dilution being employed in allergic states. With this in mind, he wrote to the Surgeon General, whose office replied "that such had been referred to the Surgeon, Fourth Service Command, Atlanta, Georgia, the medical service of that command having been designated to afford special attention to the subject of allergic states." (The quotation from that reply is very enlightening inasmuch as this reviewer, with Colonel Sanford W. French, met considerable opposition in an attempt to provide adequate diagnostic and therapeutic measures for allergic military personnel—now to find, at this late date, that the Fourth Service Command to which we were assigned, had been designated as the official service!) Histamine-like responses have been reported as properties of curare and tubocurarine when used intracutaneously and intra-arterially. Camroe and Dripps<sup>20</sup> found that typical wheals were produced when these drugs were thus used. Hypotension and bronchospasm were not affected by neostigmine because this drug overcomes only the paralyzing effect upon the neuromyal junction.

The introduction of the antihistaminic drugs, beta-dimethylaminoethyl benzhydryl ether hydrochloride (benadryl) and N'-pyridyl-N'-benzyl-N-dimethylethylene diamine hydrochloride (pyribenzamine), has resulted in the publication of numerous papers dealing with the investigative and clinical problems derived therefrom. Glowing reports originally were noted in both professional and lay works and periodicals. These were of such an optimistic trend that editorials in leading publications devoted to allergy stressed the necessity of placing a damper on the enthusiastic exploitation. It is stated<sup>37</sup> that these drugs do not offer any cure or hope of cure when used alone. The importance and frequency of "side-reactions" has been found to be almost an accepted part of the drug action. A stable, well-considered editorial stated "it is too soon, however, to give the proper evaluation of these drugs until the period of overenthusiasm has subsided and we can get more definite facts regarding the number who received unfavorable reac-

tious or who developed new forms of allergy from the use of these drugs." Another editorial<sup>36</sup> emphasized the careful consideration of the uses, limitations and dangers of these drugs. At best, these remedies produce only temporary relief, and many types and phases of allergic phenomena are not affected by these compounds.

The normal person failed to show any appreciable change in primary body functions when investigated by McGavack et al.<sup>89</sup> Using benadryl, these workers determined that the normal physiologic mechanisms of renal function, circulation, and basal metabolism remained within standard limitations. There was no change in the differential count nor in the blood chemistry in these patients. The therapeutic value of benadryl was found to be of most significance in the management of urticaria. Bowen<sup>16</sup> also stated that his results with this medication in seasonal hay fever were such that he felt it to be an excellent aid. Improvement was obtained in 60 to 70 per cent of the patients. In agreement with other opinions, Bowen found that this drug was of little help in the asthmatic patient. It can be postulated, therefore, that the patient with seasonal hay fever who depends entirely on the drug for his relief, is the victim of inadequate therapy. Pollen hyposensitization should be given concurrently. A word of warning is extended by the above author regarding the use of benadryl by the patient clinically sensitive to aspirin. Beneficial results in urticaria were the findings of Curtis and Owen<sup>28</sup> in the treatment of eighteen patients. Eleven of these received complete relief, three obtained a palliative effect described as good, and four were unaffected by the medication. One of these eighteen experienced toxic symptoms of weakness, vertigo and drowsiness. O'Leary and Farber<sup>97</sup> prescribed benadryl to be taken by mouth every three to four hours, in doses varying from 50 to 100 mg., for thirty-five patients with acute urticaria. Twenty were completely relieved, twelve were improved, while three were not benefited. Forty-eight of seventy-five patients with chronic urticaria were entirely relieved while they were taking the drug; seventeen had fewer lesions and ten were not affected. Eight of twenty-five patients with severe paroxysms of pruritis due to atopic dermatitis were relieved. Benefit was noted in only six of thirty-eight patients whose itching arose from various sources. Softening of the skin and reduction in edema was observed in two of nine acrosclerotic patients. Side-effects usually occurred during the first few days of therapy, with "late" reactions developing in only ten patients. The margin of safety and the absence of any manifestations of cutaneous sensitivity have been mentioned.

Clinical studies with pyribenzamine were done by Arbesman et al.<sup>6</sup> on 495 patients having a total of 565 allergic manifestations. The nasal congestion, discharge and sneezing of 236 patients with allergic rhinitis were relieved. There was a total of 313 patients so classified. Of 154 patients with urticaria, 128 were improved for a relief percentage of 83 per cent. Relief or prevention of dyspnea and cough was experienced by 48 per cent of bronchial asthmatics. This is decidedly higher than the results found by this reviewer in private practice. These authors felt that pyribenzamine was more effective prophylactically than therapeutically in asthma. The mechanism of action of these antihistaminic drugs is still unknown. Mayer<sup>87</sup> states the generally accepted idea is that the different antihistaminic substances compete with histamine or displace it from its point of action. Once histamine has produced its effect, the drugs are unable to reverse the reaction, but they do act to minimize the effect of any further histamine liberation. This decision of Friedlaender and Feinberg<sup>48</sup> may explain the failure of oral administration to affect some allergic states, inasmuch as insufficient amounts may reach the site of action.

Waldbott<sup>122</sup> reported sixteen of twenty patients with urticaria receiving prompt and marked relief. Five of these sixteen were given a placebo capsule without

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effect upon the urticaria. Only eight of thirty-one patients with seasonal hay fever were not relieved. The results in bronchial asthma, seasonal and perennial, were 50 per cent. Three patients suffered asthmatic attacks shortly after the ingestion of the drug and the question of spontaneous sensitivity is raised. O'Leary and Farber<sup>88</sup> used benadryl in fifty patients suffering with acute and chronic urticaria. The average length of treatment in fifteen acute patients was sixteen days, with nine receiving prompt relief and five showing improvement, with failure in one instance. The chronic patients had had their symptoms for an average duration of four years. Twenty-five obtained excellent benefit from the medication. Seven were improved and no effect was noted in three. In bronchial asthma and seasonal hay fever, Koelsch et al.<sup>78</sup> found their results to be much better in uncomplicated hay fever. Benefit was extended to thirty-nine of fifty-two patients. Relief was experienced by only four of twelve asthmatics. Combined seasonal hay fever and asthma totaled eighty-three patients, of whom fifty-seven were relieved, with the remaining twenty-six continuing to have symptoms. In treating various allergic diseases in eighteen children, Logan<sup>83</sup> determined that the optimum dosage should be 2 mg. per pound (0.5 kg.) of body weight. Williams<sup>131</sup> reported two patients with Ménière's disease who received benadryl. One of these obtained 75 to 80 per cent relief, while the other patient was unaffected by the drug.

McElin and Horton<sup>88</sup> made the following observations in the use of benadryl in seventy-four patients: (1) the cutaneous vasodilating action of histamine is reduced; (2) the nasal congestion induced by the vasodilating action of histamine is alleviated; (3) the gastric acid response to histamine may be decreased; (4) the wheal and flare response is depressed in hypersensitivity to cold. They felt that the drug was of little value in histaminic cephalalgia, in that the severity of the attacks was decreased to some extent, but the frequency persisted. They could determine no abnormal changes in blood and urine examination during the administration and use of the substance.

A reduction of anaphylaxis in dogs was produced with benadryl by Wells, Morris and Dragstedt.<sup>127</sup> There were no deaths in twenty-two animals, as compared to nine fatalities in twenty-six controls. They concluded that histamine plays a significant role in anaphylaxis in dogs. The fact that benadryl merely reduced rather than obliterated the vasodepressor effect of histamine prevents the opinion that histamine is the "only" factor in anaphylaxis. It has been published that benadryl by mouth has no consistent effect on gastric acidity in normal persons, or following histamine stimulation of gastric secretion. Because of this, benadryl should not prove of significant value in the management of peptic ulcer.<sup>115</sup> McGavack et al.<sup>90</sup> found that benadryl did produce a depressant effect on gastric acidity when given orally or by slow intravenous administration. It is their suggestion that the drug should be tried in the management of peptic ulcer.

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# \* In Memoriam \*

## ERICH URBACH, M.D., F.A.C.A.

Dr. Erich Urbach passed away suddenly December 17, 1946, in Philadelphia, Pennsylvania, from coronary occlusion. He was born in Prague, Czechoslovakia, July 29, 1893. After graduating from the Prague Grammar School and the Royal-Imperial State-Gymnasium of Prague, he attended the University of Vienna Medical



School for two years when his studies were interrupted by the first World War. From 1914 to 1918 he served in the first World War as lieutenant in the Austrian Army, and was a member of the surgical group of Professor Anton von Eiselberg. His distinctions included the golden cross of merit with crown, and the ribbon of medal for bravery, the Charles-Army cross, and the silver medal of honor from the Red Cross with the decoration of war.

Dr. Urbach graduated in 1919 from Medizinische Fakultät der Universität Wien, Vienna, Austria. He interned at the Allgemeines Krankenhaus, Vienna, and most of his postgraduate studies were at the University of Breslau, Germany, in the Department of Dermatology, under Professor J. Jadassohn. From 1921 to 1923 he was resident in internal medicine at the General Hospital in Vienna. He served at the Jewish Hospital, Vienna, under Professor Hans Koenigstein from 1923 to 1928. In 1923 he became a Fellow of the Board of Dermatology in Vienna. From 1928 to 1937

he was Assistant Chief of the Department of Dermatology and Syphilis of the University of Vienna under Professor Wilhelm Kerl. On July 29, 1929, he became Associate Professor of the University of Vienna Department of Dermatology and Syphilis. From August 7, 1936, to March, 1938, he was Chief Physician of the Department of Dermatology and Allergy, Merchants Hospital, Vienna. He came to the United States in 1938 and served until his death as Associate in Dermatology at the University of Pennsylvania, and from 1939 to the time of his death, as Chief of the Allergy Department, Jewish Hospital, Philadelphia.

He was a member of the Philadelphia Allergy Society, the Philadelphia County Medical Society, a Fellow of the American Medical Association, a member of the Society of Investigative Dermatology, a Fellow of the International Association of Allergists, and a Fellow of the American College of Allergists of which he was formerly a member of the Board of Regents. Dr. Urbach was a conscientious member of the Editorial Board of *ANNALS OF ALLERGY* which is published by the American College of Allergists. He was an Honorary Member of the Turkish Dermatological Society and the Spanish Academy of Dermatology, and a Corresponding Member of the Hungarian Dermatological Society and the Polish Dermatological Society.



## IN MEMORIAM

Dr. Urbach was associated with his wife, Dr. Josepha Urbach, in the practice of allergy and dermatology at 422 Medical Arts Building, Philadelphia, Pennsylvania. Dr. Urbach, throughout his medical career, was an indefatigable investigator. He was a prolific writer, and his contributions to the field of dermatology alone will remain as a monument to his prodigious achievements. A perusal of the titles of his 212 publications which are published in the leading medical journals of this country and abroad, including three books, shows that they are characterized by an unusual scope of subjects. The first edition of his book, *Allergy*, co-authored by Dr. Philip M. Gottlieb, was exhausted so rapidly as a result of becoming a standard textbook in many of the medical schools that a second edition with many revisions was published less than three years later. During this short time, Portuguese and Spanish translations appeared. The second edition of 960 pages presents a comprehensive yet thorough and practical treatise on all allergic diseases. It contains the most complete bibliography on the subject in any textbook here and became a ready reference for physicians all over the world who are interested in the subject of allergy.

Dr. Urbach was an untiring clinician, teacher, and investigator. He commanded the respect of his students and was generous with his time in helping the advancement of the subject of allergy. His clinics in Philadelphia were rapidly becoming the mecca for postgraduate study in allergy, and students from the Latin American and European countries attended regularly. He was very fortunate in having a patient and sympathetic wife who shared with him his professional duties. He had two sons, John and Frederick; the latter is a physician serving at the Jefferson Medical Hospital, Philadelphia.

Dr. Urbach was fearless when advancing his theories and was oblivious to criticism. He pursued a conscientious path in all his undertakings. When he first came to this country he was handicapped with the usual obstacles that confronted many of the physicians who emigrated from Europe about that time. He easily overcame these barriers by his friendliness and willingness to help all who contacted him. He is greatly missed by his family and his increasing circle of personal friends. The name of Erich Urbach will always be prominent as one of the world's leading men in the field of medicine.

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### Does the Routine Treatment of Asthma Need Revision?

(Continued from Page 131)

diets if the patient is emaciated; the resumption of Duke's method to counteract cold sensitivity by gradually building up a tolerance against sudden temperature changes; elimination of habitual medications of standard drugs, especially those administered by means of atomizers and hypodermics.

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# News Items

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## GRANT MADE AVAILABLE TO STANDARDIZATION COMMITTEE

The College is very grateful to Marcelle Cosmetics, Inc., of Chicago, for making available to the Standardization Committee \$1,500 for the continuation of research on the standardization and purification of allergens, which has been one of the functions of the College since its inception.

This fund has been accepted by the Kentucky Research Foundation, a corporation organized at the University of Kentucky for the furtherance of research, public service, and scholarships. Dr. Morris Scherago, head of the Department of Bacteriology at the University of Kentucky, is a member of the Research Committee of this Foundation. He will continue the work pioneered by Dr. George E. Rockwell and will do research, with the collaboration of Doctor Rockwell, on the purification and standardization of pollens, based upon the observation made by Doctor Rockwell and his collaborators on the purification and standardization of house dust extract, the procedure of which was published in the January-February issue.

Doctor Scherago is well trained to undertake this work in collaboration with the Advisory Council and members of the Standardization Committee.

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## SCHOLARSHIPS FOR THE NOVEMBER INSTRUCTIONAL COURSE

At the time of this writing, five \$100-scholarships for the Intensive Fall Instructional Course in Allergy, to be held under the auspices of the University of Cincinnati, have been granted by the following donors:

Two scholarships—Almay, Inc., New York.

Three scholarships—Marcelle Hypo-Allergenic Cosmetics, Chicago.

We are very grateful for these grants which will make this course available to physicians interested in allergy. The awarding of the scholarships will be based entirely upon merit and on the recommendations of the deans of the medical schools in collaboration with the Scholarship Committee. These scholarships are available to residents, interns, or any recent graduate of a medical school who has shown exceptional qualifications and interest in allergy and allied subjects.

The chairman of the Program Committee, who is in charge of these scholarships, is Dr. George E. Rockwell, R.D. 1, Milford, Ohio. All requests for scholarships should be made direct to him.

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## POLAND

Dr. M. Obtulowicz writes that they have founded a society in Poland for preventing and fighting against asthma. The idea for this society originated with Doctor Obtulowicz and Dr. J. Regula, the secretary of the Cracow Jagellonian University, who died in a concentration camp in Oswiecim. They wanted this organization to be somewhat similar to the United States Hay Fever Association or Heufieberbund von Helgeland. They held their first meeting of seventeen members in 1945 and their general meeting in 1946. The Association now has 220 members, practically all of whom are asthmatics.

The scope of the activities of the Association is very large. According to their statutes, they have a treatment center for out-patient asthmatics, distribute medicines among the poorest of them, and give them financial aid for climatic and rest sojourns. They keep statistical records of the patients and take care of those patients who receive no hospital treatment. They also started a campaign to appeal for larger food rations for the undernourished "crippled" asthmatics. They are now or-

## NEWS ITEMS

ganizing in Cracow a group of physicians who intend to become specialists in curing asthma.

The Association co-operates with the Polish Red Cross, and its members have the use of the Polish Red Cross Sanatorium at Szczawnica. This resort is the best place in Poland for curing asthma. They also apply to the authorities for aid in their fight against allergic diseases, which seem to be much more prevalent following the war. There is complete co-operation with the different institutions in reducing cases of "professional skin diseases." The out-patient asthmatics are located at a place which is subsidized by the Ministry of Health. This treatment center is the principal part of the Cure and Research Center for diseases of the working people.

The Association now is working chiefly in the Cracow district, but intends to organize the entire country for this fight. This Association has the full support of the president of Cracow University and of the Office of the Health Division of the District. Much enthusiasm has been manifested by the younger physicians who are interested in allergic diseases.

Since practically all of the libraries in Poland were destroyed, physicians are eager to receive any medical books or journals in order to build up their libraries. Most of the doctors in Poland can read English, but they lack reading material. If there are any subscribers who have any medical books or who care to present a year's subscription of any medical journal, please send them to the president of the Association, Dr. M. Obtulowicz, Starowislna 6, Krakow, Poland.

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### BELGIAN SOCIETY OF ALLERGY

In July, 1946, the Belgian Society of Allergy was founded in Brussels. Dr. Jacques Duchaine, Secretary, 102, Avenue Emile de Béco, Brussels, states:

"The Society aims at promoting knowledge of Allergy among the general practitioners and of furthering laboratory and clinical work in the field of Allergy. It will favor the establishment of special allergic wards and clinics in the general hospitals and that of specialized hospitals or clinics for the treatment of respiratory allergy."

The following officers were elected at the first assembly: President, Dr. Paul Bordet, director of the Brussels Pasteur Institute; first vice president, Professor B. Dujardin, professor of Dermatology at the Brussels University; second vice president, Dr. J. Beerens (Ghent); secretary, Dr. J. Duchaine (Brussels); treasurer, Dr. P. Amy (Antwerp); first assistant secretary, Dr. A. Drymael (Brussels); second assistant secretary, Dr. C. Gessler (Brussels).

The official journal of the Belgian Society of Allergy will be the *Acta Belgica Allergica* which will be open to local and foreign collaboration and which will publish articles of interest on allergy and review all books received.

In order to promote cordial relations with the Belgian allergists and to aid them in extending the interest and knowledge of allergy in their country, members of the College, who have written books, are asked to have their publishers send complimentary copies of the books for reviewing. Since scientific research in Belgium was practically at a standstill from 1940 to 1946, any reprints of articles on allergy, which were published in this country during the war, will be appreciated. Send the books and reprints to Doctor Duchaine for the library of the Belgian Society of Allergy.

Doctor Duchaine has extended a cordial invitation to all American allergists visiting Belgium to contact him. He will be very happy to help them in whatever manner may be of use to them.

The College cordially extends congratulations and welcome to the new Belgian Society of Allergy. It is hoped that the Society will succeed in arousing interest

## NEWS ITEMS

in allergy among the physicians of Belgium, that the Society will grow rapidly, and that the *Acta Belgica Allergica* will be a great success.

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### NATIONAL ALLERGY RESEARCH AND WELFARE FUND

The National Allergy Research and Welfare Fund was established by the College on November 3, 1946, and is being developed thoroughly. A subdivision of this foundation is functioning actively under the direction of Professor Morris Scherago, Head of the Department of Bacteriology, of the University of Kentucky, with the collaboration of Dr. George E. Rockwell, and is carrying on co-operative research on the purification and standardization of pollen extracts. The results of the first co-operative research, on the standardization of house dust, were published in the January-February issue of the *ANNALS*.

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### FALL GRADUATE INSTRUCTIONAL COURSE IN ALLERGY

Dr. George E. Rockwell, Chairman and Director of the Program Committee for the Fall Graduate Instructional Course in Allergy, sponsored by the College, has completed his schedule of instructors and their subjects. The course will be held under the auspices of the College of Medicine at the University of Cincinnati, November 3 to 8, inclusive. The faculty for the course is composed of prominent members from outstanding medical schools.

The course will include every phase of allergy, covering all domains of the body. Psychosomatic allergy also will be discussed. The importance of history-taking, the diagnostic approach and management of the various allergic diseases, and complete directions for drug therapy, including details of aerosol therapy for symptomatic relief for respiratory allergy, will be presented in detail.

Headquarters will be at The Netherland Plaza, near the medical school. Luncheons will be served in the same building in which the lectures are presented.

Negotiations are being made to have this course recognized by the Veterans Administration under the GI Bill of Rights, as was the Fall Graduate Instructional Course held in Philadelphia last November. The State of Ohio Department of Education already has approved this course.

The fee for the course is \$100. Write direct to the Secretary of the College, 423 LaSalle Medical Building, Minneapolis 2, Minnesota, for reservations for the course and hotel accommodations.

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### ARGENTINE ALLERGY SOCIETY

The Directive Commission of the Argentine Allergy Society has been renewed and now is constituted as follows: President, Dr. Federico Dumm; vice president, Dr. Miguel Agustin Solari; secretary, Dr. Alois E. Bachmann; pro-secretary, Dr. David M. Zanalda; treasurer, Dr. Rodolfo E. Monto; pro-treasurer, Dr. Ladislao Naón; vocales, Dr. Guido Ruiz-Moreno, Dr. Campolican Castilla, Dr. Lorenzo Giscaféré, Dr. Vicente Galvagno, and Dr. R. Becco.

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### NATIONAL SOCIETY FOR MEDICAL RESEARCH

An appeal to enlightened citizens to refrain from supporting antivivisection activities was issued by the American Diabetes Association at its recent meeting in Toronto celebrating the silver anniversary of the discovery of insulin.

The appeal was made on the basis of the role played by experimental dogs in the development of insulin.

The statement passed by the Association was a resolution as follows:

WHEREAS the American Diabetes Association at this meeting is commemorating the 25th anniversary of the discovery of insulin; and

## NEWS ITEMS

WHEREAS insulin has been instrumental in restoring the health and saving the lives of countless human beings suffering from diabetes; and

WHEREAS the great work of Banting and Best in discovering insulin, and the subsequent scientific investigations clarifying its actions and uses, would have been impossible without the use of dogs and other domestic animals as experimental subjects;

THEREFORE BE IT RESOLVED that the American Diabetes Association hereby testifies to the value of the use of dogs and other domestic animals for purposes of scientific research; and urges all enlightened citizens to refrain from supporting the misguided efforts of so-called antivivisectionists, who constantly try to hamper the advancement of scientific medicine.

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### GRANT FOR DERMATOLOGIC RESEARCH FUND

Luziers, Inc., manufacturers of cosmetics and perfumes, Kansas City, Missouri, have contributed another \$1500.00 to the American College of Allergists for independent investigation in the field of dermatologic allergy. This fund will continue to be under the direction of Dr. Rudolf L. Baer, Associate Attending Physician, Skin and Cancer Unit, in charge of Allergy Department, New York Post-Graduate Hospital, Columbia Hospital, and Dr. Stephan Epstein, of the Marshfield Clinic, Marshfield, Wisconsin, Clinical Associate Professor of Dermatology, University of Minnesota.

The Board of Regents, in behalf of the College, expresses its sincere gratitude in accepting this generous gift.

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Albert V. Stoesser, M.D., announces that he is now located in his new office at 1409 Willow Street, Loring Park, Minneapolis, Minnesota, where he is specializing in allergy and pediatrics. He retains his title as Clinical Professor of Pediatrics at the University of Minnesota and Director of Allergy Clinics at University Hospital and Minneapolis General Hospital.

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### Benadryl in Allergic Diseases of Children

*(Continued from Page 112)*

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# ANNALS *of* ALLERGY

*Published by the  
American College of Allergists*

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Volume 5

May-June, 1947

Number 3

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## THE USE OF INTRAVENOUS ETHYL ALCOHOL IN THE TREATMENT OF STATUS ASTHMATICUS

ETHAN ALLAN BROWN, M.D., F.A.C.A.  
Boston, Massachusetts

THE patient who has been wheezing for some hours is hungry, thirsty, tense, and tired. The dehydration and low blood sugar are remedied by intravenous glucose-saline and the tension, by sedation which, encouraging relaxation and sleep, relieves the fatigue. The antispasmodic drugs ameliorate the bronchial spasm. When epinephrine is used, the side reactions include weakness and peripheral vasoconstriction as evidenced by pallor. With aminophyllin, adverse reactions include cerebral throbbing, nausea, and vomiting, accompanied by peripheral vasodilatation as evidenced by flushing and perspiration. The sedatives recommended are frequently spasmogenic and usually respiratory depressants. In any case, it is necessary to use several types of medication, the action of which is not always consistent.

For intravenous treatment, the ideal drug, allowing for the glucose-saline in which it is administered, should be nontoxic, nonallergenic, and evenly and rapidly metabolized, so that its administration may be controlled. There should be a wide margin of safety between the pharmacologic and toxic doses. The drug should be sedative, vasodilating, and, if possible, stimulating to respiration. Ethyl alcohol, given intravenously, fulfills these and other essential criteria.

The oxidation of ethyl alcohol given intravenously is rapidly completed. Of its end products, oxygen and carbon dioxide, the latter, passing off in the lungs, acts as a respiratory stimulant. The calories are easily assimilated and immediately available, 50 c.c. of 95 per cent alcohol representing 600 calories. The sedative action can be quickened or slowed by the rate of intravenous flow. The dilatation of peripheral vessels permits the body to absorb epinephrine from any of the subcutaneous depots, due to previous injection. Additional epinephrine, in doses up to 1.0 c.c., can be added to the intravenous solution.

## INTRAVENOUS ETHYL ALCOHOL—BROWN

The pharmacology of ethyl alcohol is not complex. The toxic dose is 7.7 c.c. for each kilogram of the patient's body weight. The dose for analgesia and sleep varies from 1.5 to 3 c.c. per kilogram. Since the average dose for complete narcosis, permitting surgical interference, is 2 to 2.5 c.c. per kilogram, the margin of safety is immediately apparent.<sup>2</sup>

For the narcosis of a patient who weighs 60 kg., 120 c.c. of 95 per cent alcohol and 240 c.c. of 5 per cent glucose-saline is needed. Of this solution, 40 to 60 c.c. causes sleep which, in the majority of patients, is refreshing and marked by contracted pupils and even, steady respiration, the patient awakening in two to five hours. An occasional subject, to whom the solution has been given too rapidly or in too large a quantity, may be irrational for a slight period of time. Behan,<sup>1</sup> who studied thirty patients in whom intravenous ethyl alcohol had been used for the control of postoperative pain, states that 6 per cent had vomiting, transitory headache, and occasional, very slight hematuria. In the present series, since the doses given were much smaller, no ill effects were noted.

Just as the history of alcohol taken orally for preoperative or postoperative pain is long, the history of the use of alcohol intravenously for the same purpose is brief. Goodman and Gilman (Macmillan, 1941) give it no mention. In 1945, Verkhovskaya<sup>3</sup> reported on thirty patients, for whom it had been used for preoperative anesthesia in bone surgery. In this country, Behan<sup>1</sup> used intravenous ethyl alcohol as a postoperative sedative drug in thirty patients, in only five of whom the pain persisted to a degree requiring morphine.

For the present series, 50 c.c. of 95 per cent ethyl alcohol was added to 1,000 c.c. of 5 per cent glucose-saline. If the material is to be prepared by the physician, it is advisable to Seitz-filter the alcohol previous to use. Commercial solutions, containing 5 per cent of ethyl alcohol in glucose-saline, are available with or without added Vitamin B complex. For each patient, the initial intravenous flow was sufficiently rapid to give 100 c.c. within ten minutes, and thereafter permitted to flow from 70 to 100 drops per minute. In one of our patients, in whom the rate was less than 70 drops per minute, there was no response. In all, the intravenous injection was used twenty-five times on six patients, two of whom were hospitalized on two separate occasions.

The first patient studied had suffered from severe bronchial asthma for some years, his attacks of status asthmaticus requiring hospitalization three to four times yearly, each episode lasting from three to six weeks. He responded poorly, if at all, to subcutaneous epinephrine or to ephedrine, aminophyllin, or sedatives taken orally. His response to intravenous aminophyllin (0.5 gm.), in either glucose or sucrose with epinephrine, was variable, and usually poor. Treatment with ethyl alcohol, 0.5 per cent, given by clysis was ineffective, as was a second attempt with a 0.5 per cent ethyl alcohol solution given intravenously. The third solution, containing 5 per cent ethyl alcohol, given at 90 to 100 drops per min-

ute, caused bronchial dilatation within thirty minutes. The patient fell asleep for about fifteen minutes, after which he awakened easily, dozing comfortably over the three-hour period during which the injection was given. The effects on the patient's appearance, respiration, and mental attitude were immediately apparent. With intravenous aminophyllin and other types of drugs, the patient may be much more comfortable, although physical examination of the chest proves the bronchioles to be in a state of spasm. In this patient, the lungs were completely clear of physical signs of bronchial asthma in three hours. The relief lasted twelve hours, after which epinephrine gave no relief, indicating further intravenous injection of the same solution. In all, the patient received four injections and was discharged free of asthma, his remission lasting four weeks. During hospitalization on a second occasion, a 5 per cent solution of ethyl alcohol in glucose-saline again proved efficacious for a severe attack, the symptom-free period lasting twelve hours.

The second patient was admitted in severe status asthmaticus and did not respond to epinephrine by injection or to ephedrine and other drugs taken orally. The patient was in extreme spasm, with cyanotic lips, fingers, and toes. In the past, he had responded to intravenous aminophyllin. A 5 per cent ethyl alcohol solution in glucose-saline was used, and within thirty minutes, the cyanosis was replaced by a warm, normally dry, normally pink flush and sound sleep, associated with a drop in the minute respiratory rate from 40 to 27.

Two successive intravenous injections on the two succeeding days had similar results, the patient being discharged symptom-free. Inquiries showed him to be free of symptoms for the succeeding six weeks.

The remaining patients required from three to five intravenous injections, the response being similar in each. In one patient, the solution given slowly had no effect and aminophyllin was effectively substituted. In another, upon a second admission two weeks following the first, the solution was without effect when given at the rate of 70 to 80 drops per minute, but effective within fifteen minutes when the rate was increased to 100 to 110 drops per minute. The patient, who went to the hospital in severe status asthmaticus, was able to walk home four hours following his admission.

In summary, a 5 per cent ethyl alcohol solution in physiologic 5 per cent glucose-saline, with or without epinephrine 1:1,000 (0.3-1.0 c.c.), given intravenously at the rate of 80 to 100 drops per minute, effectively relieved severe bronchial asthma in five of six patients, who did not respond to the usual medications given by the oral, subcutaneous, and intravenous methods. Two of the patients responded similarly on two successive hospital admissions. No ill effects were anticipated or observed.

The remaining data and the detailed protocols will be part of a subse-

*(Continued on Page 273)*



## CONTINUOUS INTRAVENOUS AMINOPHYLLIN THERAPY IN STATUS ASTHMATICUS

LT. ROBERT J. GOODALL, MC, AUS, and LEON UNGER, M.D., F.A.C.A.  
Chicago, Illinois

**I**N some patients with status asthmaticus symptoms continue despite various accepted methods of treatment. Wheezing, dyspnea, cough and orthopnea persist, and, in addition, loss of strength, weight and morale may also occur. It is with this type of patient that we are here concerned.

Efron<sup>3</sup> first mentioned the use of aminophyllin in asthma, but Herrmann and Aynesworth<sup>4</sup> popularized its use. In 1937 they reported favorable results in status asthmaticus by intravenous injections of 0.25 to 0.5 gm. aminophyllin dissolved in physiological saline solution. Their excellent results have been verified by numerous investigators, including one of us (L. U.<sup>7</sup>). The drug is also useful when given in rectal suppositories, as introduced by Dees,<sup>2</sup> or when instilled in the rectum (10 grains of aminophyllin with 20 c.c. tap water), as suggested by Barach.<sup>1</sup> We have found the oral use of this drug rather ineffective, and nausea frequently occurs.

It is therefore a well-established fact that the intravenous administration of aminophyllin gives more or less quick relief to most asthmatic patients, including some with status asthmaticus. The drug probably relaxes bronchial muscles and allows more air to pass through, as shown by Young and Gilbert,<sup>8</sup> Sollman and Gilbert,<sup>6</sup> and others.

The intermittent intravenous and rectal administration of aminophyllin is standard procedure at Wesley Memorial Hospital. On admission in a severe attack the asthmatic patient usually receives an intravenous injection of 0.25 gm. ( $3\frac{3}{4}$  grains) dissolved in 10 c.c. diluent, given slowly through a 10 c.c. syringe. He is then given 0.5 gm. ( $7\frac{1}{2}$  grains) intravenously, dissolved in 1,000 c.c. of 5 per cent glucose, over a period of three to four hours. This liter infusion is repeated daily for three or four days if necessary. The rectal suppositories or solution are usually given at night. In addition, in severe cases, another 10 c.c. ( $3\frac{3}{4}$  grains) are often injected intravenously at night. Epinephrine is avoided in patients with tachycardia, restlessness or pallor. Morphine is never used.

The above regime is open to criticism because:

1. The patient may need four or even more injections of aminophyllin in twenty-four hours.

Read at the meeting of the American College of Allergists, San Francisco, California, June 28 to 30, 1946.

Dr. Goodall was formerly an intern at Wesley Memorial Hospital, Chicago, Illinois.

Dr. Unger is Attending Physician at Wesley Memorial and Cook County Hospitals, Chicago, Illinois.

The aminophyllin used was furnished through courtesy of G. D. Searle Co., Chicago, Illinois.

The authors are grateful to Dr. Andrew de Roeth, also of Wesley Memorial Hospital, and several other interns, for invaluable assistance in carrying out the procedure.

# INTRAVENOUS AMINOPHYLLIN THERAPY—GOODALL AND UNGER

TABLE I. CONTINUOUS INTRAVENOUS AMINOPHYLLIN THERAPY IN  
STATUS ASTHMATICUS

INDICATIONS.	Hospitalized patients in whom previous measures, including intermittent injections of aminophyllin, have failed.
AMOUNT OF AMINOPHYLLIN PER LITER:	(a) 1.0 to 1.5 grams, depending upon severity of symptoms. (b) Gradually reduced as symptoms decrease.
VEHICLE USED:	First, 5 per cent glucose in distilled water. Second liter, 0.9 per cent saline in distilled water, then alternate.
RATE OF FLOW:	28 drops per minute— 1 liter in twelve hours. 2 liters in twenty-four hours.
EQUIPMENT:	(a) 23 gauge, short bevel, 1½ inch needle. (b) Aminophyllin, 0.50 grams in 20 c.c. or 2.0 c.c. ampules. (c) Rubber tubing with clamp. (d) Liter flasks. (e) Adhesive strips.
SITE OF INJECTION:	Broad volar or dorsal surface of forearm, avoiding joints.
PRECAUTIONS:	(a) Flask must not run dry. (b) If vein becomes inflamed, transfer to another vein.
TOXIC EFFECTS:	None observed.
DURATION OF TREATMENT:	Average 7-14 days.
RESULTS:	Good to excellent in most cases. Relaxation usually occurs. Reduces need for other methods of treatment, e.g., ether in oil, epinephrine, fever therapy and anesthesia.

2. If the onset of an attack is sudden and severe, much time may be lost before the injection can be given.

3. If the attack is well established before treatment is instituted, the response may be delayed or diminished.

With these facts in mind, we felt that if we could keep the bronchial musculature relaxed by a continuous infusion of aminophyllin we could accomplish two purposes. First and most important, the patient could be kept free from the prolonged suffering and apprehension so common in status asthmaticus. Second, the relaxation could be continued over a period of time long enough for the associated edema of the bronchial mucosa to subside and thus hasten recovery. We were also influenced by the startling results frequently obtained by the continuous intravenous administration of penicillin (Priest<sup>5</sup> and others) in subacute bacterial endocarditis.

## TECHNIQUE

The technique used is summarized in Table I. We began by calculating twenty-four hour dosage of aminophyllin used in previous treatment. With this as a guide we dissolved the total amount in 2,000 c.c. of 5 per cent glucose in distilled water. This was then given by the continuous intravenous drip method at the rate of 28 drops per minute or 1,000 c.c. per twelve hours. At no time during the procedure did we allow the treatment to be discontinued. If at any time the vein containing the needle showed evidences of inflammation the needle was transferred to another vein, preferably in another extremity. We used the broad volar and dorsal surfaces of the forearms, avoiding the joints as much as possible. This permitted the patient to use the extremity to a limited degree. Number 23 short-bevel needles are recommended. Aminophyllin in the form of the

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TABLE II. CONTINUOUS INTRAVENOUS AMINOPHYLLIN THERAPY DOSAGES AND RESULTS OF TREATMENT

Cases	Name	Sex	Age	Duration Asthma (years)	Total Grams Aminophyllin	Number Days	Results
1	H.R.	M.	33	14	19.75	14	Excellent
2	W.M.	M.	48	1.5	29.50	21	Fair
3	B.T.	F.	66	20	11	6	Good
4	R.S.	F.	25	15	13.5	20	Excellent
5	A.S.	F.	66	10	8	7	Excellent
6	M.M.	F.	61	1.5	22	11	Fair
7	A.H.	F.	39	2	12.5	8	Fair
8	M.C.	F.	37	1	12	7	Excellent
9	V.W.	F.	53	14	4	3	Fair
10	J.M.	F.	37	37	14	8	Poor

large 0.5 gm. ampules in 20 c.c. of saline may be used, but the small 2 c.c. ampules ordinarily used for intramuscular injections are satisfactory and more economical. Bed rest is necessary but diet trials can be made.

The dosage of aminophyllin was determined by the measure of relief and control of symptoms. It was necessary in all cases to begin with large doses and then gradually decrease as relief occurred. Careful clinical examinations were made several times a day, and the blood pressure and pulse were frequently recorded. No toxic reactions occurred in this series.

## CASE REPORTS

The following case reports are given in order of admission to the hospital (Table II).

*Case 1.*—H. R. a white man, aged thirty-three years, had attacks of severe bronchial asthma for fourteen years. His asthma was not controlled during a period of three weeks in this hospital. His attacks were of the most severe type, with sudden marked dyspnea, orthopnea, coughing, wheezing, and cyanosis. It was necessary to give him as many as eight or ten separate injections of aminophyllin per twenty-four hours, in dosages of 0.25 to 0.75 gm., depending on the severity of attacks. He was hardly able to eat or sleep and had lost about 10 pounds since admission. He had also received injections of epinephrine, intravenous administration of typhoid vaccine, ether in oil per rectum, and aminophyllin by mouth and per rectum. He had previously received very little relief from bronchoscopic aspiration and from deep ether anesthesia.

Three grams of aminophyllin were dissolved in 2,000 c.c. of 5 per cent glucose in distilled water and given intravenously and continuously at the rate of 28 drops per minute. Response was good. One mild attack occurred during the first twelve hour period. Wheezing practically disappeared on the fourth day and the daily dosage of aminophyllin was therefore reduced from 3 to 2 grams; on the tenth day the dosage was again decreased to 1 gram per twenty-four hours, on the twelfth day to 0.5 gram, on the thirteenth day to 0.25 gram, and then discontinued entirely on the next (fourteenth) day. He received a total of 19.75 grams. The patient's

response was remarkable, and he left the hospital three days later. There was no significant change in blood pressure throughout the fourteen days of continuous therapy, and the pulse decreased from about 150 to about 70. The patient experienced no undue discomfort; a steady decrease in cough and expectoration was noted, with slight drowsiness. The needle was changed five times, but there was no venous thrombosis. Re-examination, six months later, revealed excellent condition, with a gain of about 30 pounds. He has resumed his very arduous occupation, a telegraph linesman, and is able to climb telegraph poles without dyspnea.

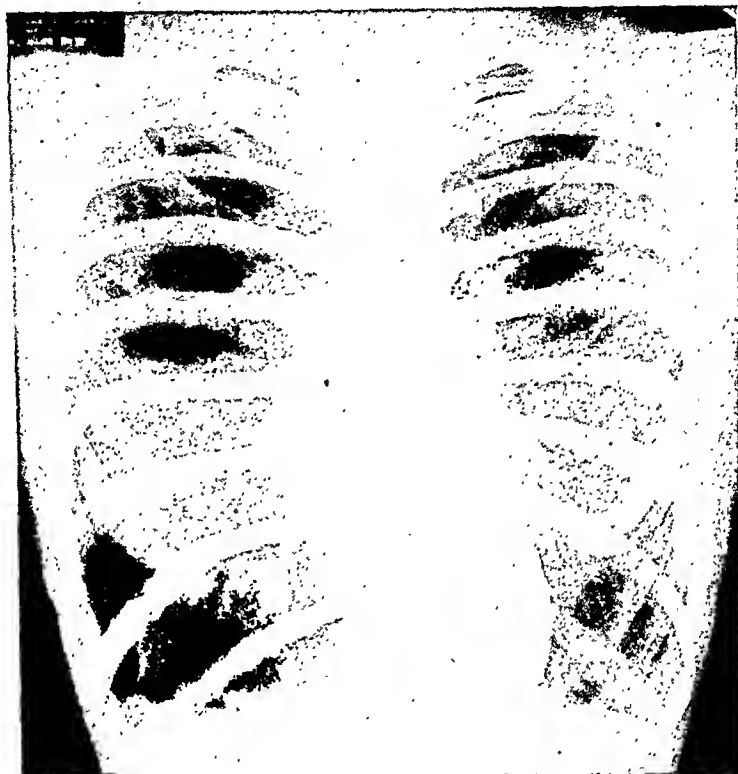


Fig. 1.

*Case 2.*—W. M., a man, aged forty-eight years, with severe bronchial asthma for about eighteen months, left this hospital three weeks previously and returned with severe asthma. He could hardly eat or sleep. Previous treatment with penicillin, sulfonamides, ephedrin, epinephrine, aminophyllin, typhoid vaccine, and ether in oil had failed. Continuous intravenous aminophyllin therapy was started with an initial daily dose of 2 gm. in 2,000 c.c. of 5 per cent glucose in distilled water. After three days 1.5 gm. were used; on the fifth day the dosage was reduced to 1 gm. but wheezing returned and the dosage was increased again to 1.5 gm., then lowered on the seventh day to 1 gm.; 0.5 gm. was given on the eighth and ninth days. At this point the vein was somewhat inflamed and the asthma was much lessened. Aminophyllin was therefore stopped. The blood pressure showed a slight fall during this nine-day period, but the pulse was not altered. No toxicity occurred. Large nasal polyps were removed at this time, and the patient left the hospital on the sixteenth day. Wheezing had practically disappeared, but asthma returned a few days later. He re-entered the hospital and received another 14.75 grams in a twelve day-period, for a total of 29.50 grams in twenty-one days. He improved again but was not completely free from asthma when he left the hospital.

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*Case 3.*—B.T., a woman, aged sixty-six years, had severe chronic asthma for over twenty years, with numerous previous admissions to this and other hospitals. She had received epinephrine, penicillin, ephedrine, sulfonamides, typhoid vaccine, ether in oil, x-ray treatments, and many injections of aminophyllin. She was admitted in acute distress, with cyanosis, dyspnea, orthopnea, cough and wheezing. She received a total of 11 grams of aminophyllin continuously over a period of six days, with considerable improvement. But a moderately severe thrombosis of the vein occurred on the fourth day, and the patient was very uncooperative; therapy was discontinued much too soon. Her asthma is now mild but still present.

*Case 4.*—R. S., a woman, aged twenty-eight years, had severe bronchial asthma for fifteen years, with previous admissions to this and other hospitals. She was very apprehensive and had severe asthma. Marked emphysema was present, and she weighed only about 70 pounds. X-ray confirmed the diagnosis of asthma and emphysema and also showed three small areas of spontaneous pneumothorax (Fig. 1). On previous admissions she had received penicillin, epinephrine, typhoid vaccine, and aminophyllin by various routes.

Continuous intravenous aminophyllin therapy was begun with 1 gm. each day for two days, and decreased to 0.75 gm. on the third day; mild wheezing returned and the dosage was increased to 1.5 gm. on the fifth day; symptoms were again well controlled, and dosages were decreased to 1, 0.5, and 0.25 gm. on the seventh, eighth, and ninth days, respectively. Wheezing disappeared and continuous therapy was discontinued in favor of occasional injections of epinephrine and the use of aminophyllin per rectum. Symptoms reappeared in mild degree four days later, and continuous therapy was resumed, beginning with 2 gm. for each of four days, followed by 1.5 gm. on the fifth day, 1 gm. the sixth and seventh days, 0.5 gm. the eighth and ninth days, and 0.25 gm. the tenth and eleventh days. She had a total of 13.5 gm. of aminophyllin during twenty days. The needle was changed several times but no thrombosis occurred. She left the hospital in good condition, with only an occasional mild episode of asthma. She was put on a high-carbohydrate, high-caloric, high-salt diet, plus injections of adrenal cortex extract, and has gained over 30 pounds.

*Case 5.*—A. S., a woman, aged sixty-six years, with severe bronchial asthma for ten years, was semi-stuporous when first seen. She had previously received epinephrine and two injections of morphine; as a result breathing was almost absent and her condition was serious. She was given 0.25 gm. aminophyllin intravenously and was hospitalized. She received 8 gm. aminophyllin during seven days of continuous therapy, with prompt relief of symptoms. Tachycardia disappeared, the blood pressure was slightly reduced. Wheezing was absent when she left the hospital. Since then she has had mild asthma at times, with symptoms easily controlled by occasional use of aminophyllin, epinephrine, or ephedrine.

*Case 6.*—M. M., a woman, aged sixty-one years, had very severe asthma for about twenty months, with little relief from previous measures, including intermittent use of aminophyllin, sulfonamides, typhoid vaccine, iodides, apomorphine, and "Gay's" treatment. Continuous intravenous aminophyllin therapy was given for eleven days, with a total of 22 gm. of the drug, but results were only fair. Some wheezing persisted. Bronchoscopic aspiration was then tried but with little relief, and the patient left the hospital with only a little improvement. No toxicity was noted.

*Case 7.*—A. H., a woman, aged thirty-nine years, with chronic severe asthma for two years. She received 12.5 gm. aminophyllin by the continuous method over a period of eight days. No reactions occurred, and she left the hospital moderately improved. Asthma returned in full force after she returned home.

*Case 8.*—M. C., a woman, aged thirty-seven years, had asthma for about a year and a particularly severe attack before entrance to the hospital. She was given 12 gm. dissolved in 14 liters of glucose or saline during seven days. Asthma disappeared entirely, and she has been practically asthma-free since she left the hospital.

*Case 9.*—V. W., a woman, aged fifty-three years, had asthma for fourteen years. She received only 4 gm. of aminophyllin during three days and refused further treatment because she did not like the procedure. She left the hospital three days later, with fair results.

*Case 10.*—J. M., a woman, aged thirty-seven years, had chronic asthma almost from birth. She received 14 gm. of aminophyllin during eight days, without much relief.

# DISCUSSION

Ten patients in status asthmaticus received continuous intravenous aminophyllin therapy. Relief was obtained in almost all cases, with brilliant results in four patients and failure in only one. Relapses occurred in some cases, as was to be expected, as aminophyllin is not a cure-all. Initial dosages varied from 1 to 3 gm. of aminophyllin dissolved in 2,000 c.c. per twenty-four hours, and dosages were decreased as improvement occurred. Dosages were temporarily increased in two of the patients when wheezing recurred, and in each case wheezing quickly disappeared. In these patients we probably reduced amounts too rapidly; a longer, more sustained period with larger amounts of aminophyllin will probably bring more lasting relief. Toxic symptoms were entirely absent. The blood pressure and pulse declined as the asthma disappeared.

Inflammation of the vein occurred in two cases but disappeared in a few days. Similar thrombosis has occurred with continuous intravenous penicillin therapy. We began by using only 5 per cent glucose solution but we now alternate liters of glucose and of physiological salt solution. The salt solution is less irritating but we like to use 5 per cent glucose because it is almost as free from irritation and it is nutritious (50 gm. per liter); glucose is also very helpful to a liver from which glucose may have been driven by frequent administration of epinephrine. We shall continue to use glucose for intermittent injections when we give aminophyllin over a three to four hour period. The incidence of thrombosis of the veins can also be lessened by attention to three small details. The needles should have short bevels; they should be firmly taped in place and the tapes checked at frequent intervals to insure firmness; and the needle should be changed to another vein at the earliest sign of inflammation. The solution must not be allowed to "run dry."

No blood level determinations for aminophyllin were made, as we were unable to find a quantitative method of determination, and to our knowledge one does not exist.

It is important, of course, to use all possible means to find and eliminate the cause of bronchial asthma; hyposensitization continues to be of extreme importance. But when specific measures fail and the usual non-

specific methods are also unsuccessful, we urge others to try continuous intravenous aminophyllin therapy.

#### CONCLUSIONS

1. Status asthmaticus in ten patients was completely or partially eliminated in nine cases by the continuous intravenous administration of aminophyllin. Relapse may or may not occur when the procedure is discontinued.

2. Dosage consisted of up to 2 or even 3 gm. of aminophyllin dissolved in 2,000 c.c. of 5 per cent glucose in distilled water or of physiological salt solution, alternating; the solution was given at the rate of 28 drops per minute.

3. Large dosages of the drug should be used initially and very gradually reduced as the asthmatic symptoms subside.

4. Aminophyllin can be given in dosages up to 3 gm. per twenty-four hours without undue danger to patients with severe bronchial asthma.

5. Continuous intravenous aminophyllin therapy is strongly recommended for the most severe types of status asthmaticus, the types which have resisted all other kinds of therapy.

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#### TOXIC THROMBOCYTOPENIC PURPURA FOLLOWING LOCAL SULFATHIAZOLE THERAPY. Donaldson, G. M., and Scarborough, H.: *Arch. Dis. Childhood*, 20:69, (June) 1945.

The author describes the case of a boy twelve years of age treated with 5 per cent sulfathiazole ointment twice a day because of a mild impetigo. Epistaxis and a generalized purpuric rash started the evening of the second day. On the third day the platelets were reduced to 20,000 per c.mm. and capillary resistance was greatly reduced. There was no history of allergy or of blood dyscrasia in the boy or his family and he had never previously had sulfonamide therapy. Recovery occurred on discontinuance of the sulfathiazole ointment and daily transfusion for five days. After return of the platelet count and capillary resistance to normal levels the application of sulfonamides to the intact skin produced striking reductions in capillary resistance at and away from the site of application. Less striking falls in platelet counts were noted. The author considers that these observations point to the importance of the vascular factor (low capillary resistance) as the basis of toxic thrombocytopenic purpura.

## CUTANEOUS REACTION-UNITS

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A REACTION resulting from a cutaneous test is defined as *a wheal surrounded by an erythema*. Both parts of the reaction express its intensity but there is no constant relation between the two. For example, it is found, selecting from a series of fifty-two tests made by the intradermal injection of 0.01 c.c. of pollen extracts of varying concentration, that reactions showing wheals 10 mm. in diameter may be surrounded by erythemas measuring 35 to 60 mm. in diameter. Also from a similar series of reactions, erythemas of 40 mm. in diameter may surround wheals ranging from 6 to 12 mm. in diameter.

It is in recognition of this dual nature of the cutaneous response that the method of visual estimate, expressed by strings of plus signs to indicate "size," has come into general use. The method has in its favor the possibility of giving consideration to both the wheal and erythema in rating the "size" or intensity of a reaction, an advantage which is denied to mensurative methods of recording the reaction at present in use. Unfortunately, however, records made in this way are necessarily subjective and express little more than the emotional and possibly biased response of the observer to his observation.

That there is a quantitative relationship between the excitant and the skin response is to be expected. Indeed such has been shown by several investigators. Harley (1937) showed that in comparative cutaneous tests, if the diameter of the wheal of one were double that of another, it would indicate a potency value of ten or fifteen times in the excitant; or if three times the diameter, it might indicate a potency ratio of twenty times.

Owing to the extreme variability in sensitivity of different sites on the human skin, the most successful use that has been made of the reaction size has been by direct comparison of reactions at comparable sites and far enough apart so that the reactions do not influence each other. Thus Bowman (1934, 1935) was able to distinguish antigenic solutions differing by as little as 25 per cent, providing the compared tests were made 4 inches apart vertically or 1.5 inches horizontally on the upper arm. Pabst, Boatner and Efron (1940) showed that, from a statistical analysis of an adequate number of samples (501), parallel comparative skin tests on the radial and ulnar sides of the forearm showed a significant difference when the exciting substance on the one was twice the strength of that on the other. But when the antigenic strengths were the same in the two positions, there was no significant difference. The observer in such cases has only to decide which, if either, of two reactions is the

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larger. The personal element is here eliminated by keeping the observer in ignorance of the values of the testing materials and not asking him to tell how much larger one reaction is than another.

TABLE I. AVERAGE DIAMETER, IN TWELVE TESTS, OF  
WHEELS (W) AND ERYTHEMA (E) AND THEIR  
CORRESPONDING REACTION VALUE (E-W)W

Serum Dilution	w	e	(e-w)w
1:10	12.58	47.08	434
1:20	11.83	48.33	432
1:40	11.58	45.83	397
1:80	11.08	43.33	357

Though these three examples, selected from a considerable number recorded in the literature, serve adequately to show that there exists a relation between the strength of the antigen and the intensity of the reaction, I find no report that indicates numerically what this relation may be, closer than that of Harley.

In order to evaluate the cutaneous response in terms of antigenic strength, it is necessary to have a means of measuring the former, comparable in accuracy with the simple method of determining relative strengths of antigen by dilution. For simplicity the cutaneous response may be regarded as the product of two variables, the wheal and erythema. In this sense it is two-dimensional, but these dimensions are curiously related. If the erythema is increased while the wheal remains constant, the reaction value will be increased in proportion indefinitely. If the wheal is increased while the erythema remains constant, however, the reaction value is increased only up to the point where the wheal begins to encroach on the erythema. The wheal's further increase causes the reaction value to diminish, reaching zero when the wheal coincides with or obliterates the erythema, for a wheal without erythema is not a reaction. For example, it is found that intradermal injections of 0.01 c.c. sterile saline regularly give wheals 4 to 7 mm. in diameter, and those of 0.05 c.c. give wheals of 10 mm. or more in diameter, but these are without erythemas so their reaction values are zero.

If the wheal and erythema are regarded as of equal value, the point of encroachment upon the erythema by the wheal is where the diameter of the latter becomes greater than one-half of the over-all diameter of the former, in other words, greater than the excess of the erythema over the wheal.

Accordingly, I have chosen the unit of cutaneous reaction as a wheal 1 mm. in diameter, surrounded by an erythema with a diameter of the same amount in excess, that is to say of 2 mm. in over-all diameter. Any increase in the erythema, or of the wheal together with the erythema, providing the former does not encroach on the latter, denotes a proportionate increase in the intensity of the reaction.

Making use of this unit, cutaneous reactions may be simply expressed by multiplying the wheal diameter by the excess of the erythema diameter over that of the wheal in millimeters. Thus  $(e-w)w = n$

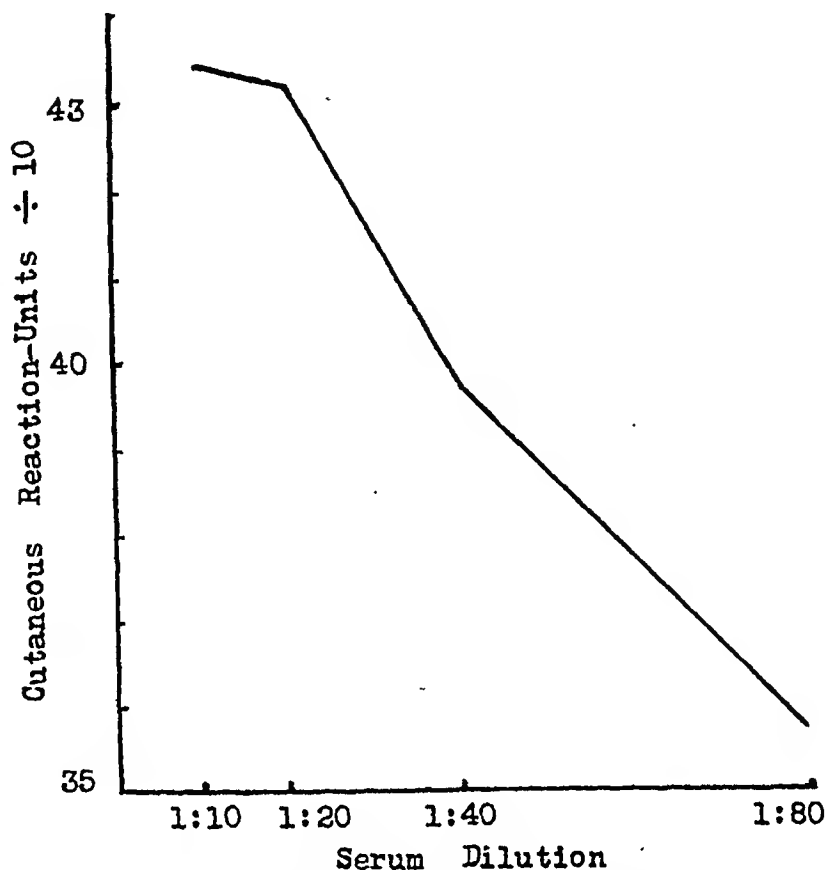


Fig. 1. Serum L. G. Dilution Curve. Reactions of sensitized sites to 0.01 c.c. mountain cedar, 100 units per c.c. Average of twelve recipients.

In this equation  $c$  equals the over-all diameter of the erythema,  $w$  equals the diameter of the wheal and  $n$  equals the number of cutaneous reaction-units. Expressed in this way, the unit reaction becomes  $(2-1)1=1$ . A reaction with twice the wheal and twice the erythema becomes  $(4-2)2=4$ , or with ten times the wheal diameter and ten times the erythema diameter, it becomes  $(20-10)10=100$ .

The increase by squares in the value of  $n$ , of course, accrues from the two-dimensional character of the response. If the reaction is regarded as one-dimensional, as it could as well be, the unit-reaction would be expressed as  $\sqrt{(2-1)1}=1$ , and a reaction with the wheal and erythema both twice as large would become  $\sqrt{(4-2)2}=2$  or, with both parts increased ten times, would be  $\sqrt{(20-10)10}=10$ . It seems that this treatment would unnecessarily complicate the calculations, so for the present studies I have chosen to regard the reaction as two dimensional.

# CUTANEOUS REACTION-UNITS—WODEHOUSE

TABLE II. REACTIONS OF SITES SENSITIZED TO  
J.B. SERUM OF VARIOUS DILUTIONS

Dilution	1:50		1:100		1:200		1:400	
Recipient	w	e	w	e	w	e	w	e
VK	10	50	9	50	10	60	9	40
MC	12	50	8	45	9	40	9	30
AB	10	40	11	55	9	40	8	50
Average	10.7	47	9.3	50	9.3	47	8.7	40
Reaction Units	388		378		351		272	
Dilution	1:125		1:250		1:500		1:1000	
FM	9	15	9	15	6	0	7	0
FF	10	40	10	55	8	30	7	25
BM	10	60	8	40	7	45	6	0
Average	9.7	38	9	37	7	25	6.7	8.3
Reaction Units	274		252		126		107	

It should be borne in mind that the use of two dimensions in establishing this unit is purely a mathematical concept and does not attempt to present a complete picture of the cutaneous reaction. The wheal alone is three dimensional; Abramson and Gorin (1939) have pointed out that its thickness during development varies to some extent independently of its length or breadth. Moreover, Lewis (1927) has shown that the reaction as a whole is a triple response, consisting of a red reaction, a wheal and erythema. We are not concerned with the red reaction because it is quickly obliterated by the wheal, but before this has happened there appears an erythema or flare, as called by Lewis, which is replaced or extended by a flare which later results from the development of the wheal. However, for practical purposes, it appears that the average diameter of the wheal and of the final erythema may suffice.

## APPLICATIONS

Those who have studied the phenomena of local passive transfer have found that the serum from a sensitive individual used to sensitize the skin of a normal recipient may be diluted several to many times and still produce reactive sites. Moreover, as would be expected, the size of the reactions obtainable from these sites declines as the concentration of the serum is reduced. This was first observed by Levine and Coca (1926) who recorded the sizes of their reactions by means of ink tracings of the wheals and erythemas. These showed that both declined continuously with the decreasing serum concentration.

Their experiments have here been imitated, substituting measurements in terms of the unit just described for their ink tracings. The serum of a patient sensitive to the pollen of mountain cedar was used in dilutions of 1:10, 1:20, 1:40 and 1:80. Sites were sensitized on each of twelve recipients with the four dilutions by the intradermal injection of 0.05

c.c. of each. Four sites were chosen as uniformly placed as possible in each recipient. There were two on each upper arm, four or more inches vertically apart and symmetrically placed on opposite arms. Dilution

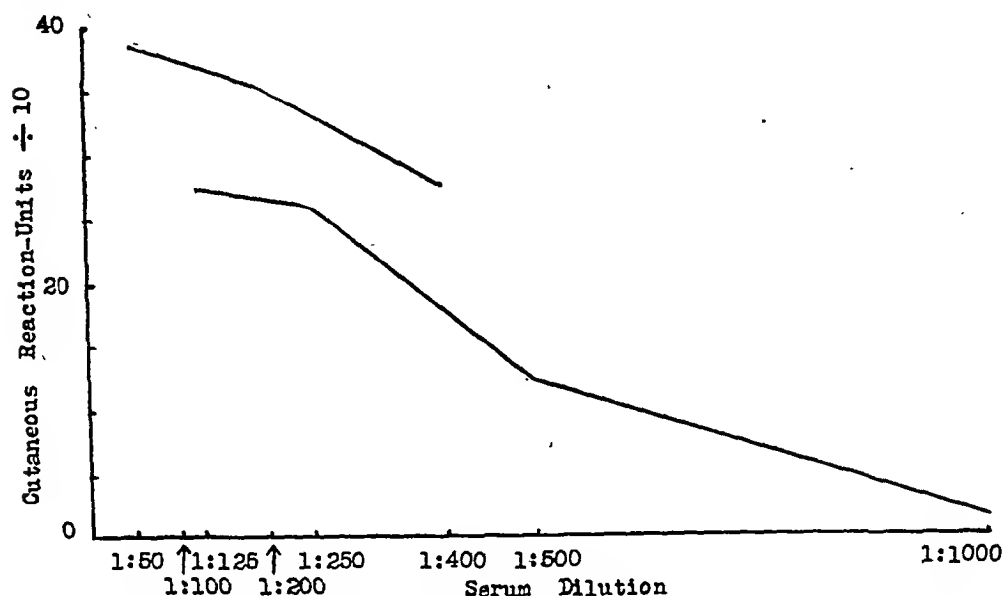


Fig. 2. Serum J. B. Dilution Curves. Reactions of sensitized sites to 0.01 c.c. timothy, 100 units per c.c. Averages of three recipients each.

1:10 was always placed opposite 1:40—in five of the recipients in the upper positions and in seven on the lower. Dilution 1:20 was always placed opposite 1:80—in five of the recipients in the lower positions and in seven in the upper.\*

This was done to equalize any consistent differences that there might be between the upper and lower positions. Three days later all sites were tested with 0.01 c.c. of 100-unit mountain cedar pollen extract. The average diameters of the wheals and erythemas are shown in Table I (columns 2 and 3).

Both parts of the reaction are found to decline, on the average, with the diminishing concentration of the serum, except the erythema from the 1:20 dilution which rises slightly. However, when the reactions are expressed in terms of cutaneous reaction-units, all decline with the serum-concentration. These relations become quite clear when the values of the cutaneous reactions and antigenic concentrations are plotted co-ordinately (Fig. 1). The tendency of the curve to flatten at the top shows that any further increase in the serum concentration would probably not produce a much larger reaction with the antigenic concentration used. On the other hand, if the curve is projected in the opposite direction, it is roughly estimated to reach the level of zero-reaction at about two more steps in the dilution series or at a dilution of 1:320.

\*The experiment was planned to include fourteen recipients with seven sensitized in each pattern, but some of the sensitized sites were lost on two recipients.

The serum of another patient, sensitive to timothy, was examined for reagin content. From a preliminary short series dilution test it had been estimated that the reaginic activity of this serum would vanish at a dilution of about 1:1,000. Two sets of dilutions were made, 1:50, 1:100, 1:200, 1:400 and 1:125, 1:250, 1:500, 1:1,000. Three recipients were used for each set. Sites were chosen on the upper shoulder and scapula. These were sensitized in the first group of three with dilution 1:50 opposite 1:200 and 1:100 opposite 1:400, in the second group with 1:125 opposite 1:500 and 1:250 opposite 1:1,000. No further attempt was made towards adjustment of positions since these appear to yield no consistent irregularities in value. Three days later, all sites were tested with 0.01 c.c. of timothy, 100 units per c.c. (Table II). Although there is considerable irregularity in the sizes of the wheals and erythemas, when these are averaged for the three recipients in each group and their reaction values plotted (Fig. 2), they assume a rather orderly arrangement. The two curves are approximately parallel so that they are mutually confirmatory. The fact that they are at different levels indicates that the average susceptibility of one group of recipients was higher than that of the other, the result of the well-known individual variation in human skin sensitivity.

Besides the examples in serum dilution given above, the cutaneous reaction-unit has been found a convenient means of measuring and graphically recording the effect of antigen dilution on the intensity of the reaction, the reverse effect of antigen dilution on the retest reactions in both *in vitro* and *in vivo* neutralization tests, and on the effect of the time intervals between sensitization and testing. It offers a simple numerical system of recording reaction intensities.

## SUMMARY

Cutaneous reaction-units may be expressed as  $(e - w)w = n$  if  $n$  equals their number and  $e$  and  $w$  the diameters of the erythema and wheal, respectively, of a cutaneous reaction.

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## TREATMENT OF INSULIN ALLERGY

### With Report of a Case

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SINCE the discovery of insulin and its use in the treatment of diabetes mellitus, numerous reports of allergic reactions to the commercial product have been reported. Only a small percentage of these cases were proven to be definitely due to crystallin insulin.<sup>10,22</sup> In reviewing the literature written on the subject, it becomes obvious that most reports have been concerned mainly with presenting evidence of the existence of insulin allergy. The methods of treatment of these cases have been quite varied and in the majority of the cases, unsuccessful. Too few have been concerned with the underlying immunologic principles. The reason is quite evident when we realize that the incidence of insulin allergy is rather small. The reported incidence of allergic response to insulin varies from .04 to 30 per cent. Collens, Lerner and Fialka<sup>5</sup> reported that out of 407 cases of insulin treated diabetics, 7.3 per cent showed protein reactions. Hallerman<sup>8</sup>, in a total of 541 diabetics treated with insulin, found only two cases with allergic symptoms severe enough to warrant discontinuance of insulin therapy and he concluded, therefore, that insulin allergy was so rare as to cause little concern. Allen and Scherer<sup>1</sup>, in their review, conclude that of all cases sensitive to insulin only 1 to 2 per cent will show systemic reactions manifested by urticaria, edema, pallor, flushing, fall in blood pressure, circulatory collapse, and gastro-intestinal symptoms. The other 98-99 per cent manifested mild to severe local reactions at the site of the injection. Yasuna<sup>22</sup>, in his review concludes that "since the severity of the disease in persons developing diabetes in the fifth to seventh decades often is mild, and since the great preponderance of cases showing generalized allergy to insulin were in the older age groups, the problem of insulin therapy is not as acute as in the young age group. Therefore, it is possible to discontinue insulin in many patients showing generalized sensitivity to the medication."

The above figures and conclusions clearly indicate the reason for the tendency to treat the problem of insulin allergy as little more than a curiosity and to treat the individual case by withdrawing the medication. That is all very well in the patient who can be controlled on diet alone. But what of the occasional young or old diabetic who must have insulin? That person, I am sure, will not be satisfied with statistics and will demand that something be done for him. Bayer's case<sup>2</sup>, following the administration of 5 units of insulin developed severe abdominal cramps, generalized eruption and a "sense of choking." Herold<sup>11</sup> reports the

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## INSULIN ALLERGY—BURDEN

case of a twenty-three year-old diabetic who after 20 units of insulin developed severe urticaria, angioneurotic edema and "asthmatic wheezing and choking sensation," necessitating the repeated administration of epinephrine. Allen and Seherer's<sup>1</sup> case was that of a forty-eight year-old woman who after the administration of insulin developed urticaria and angioneurotic edema of the face, mouth and throat to such a degree that breathing became difficult and she was in great distress. These authors also mention in their report several reported cases in which failure of insulin to exert its usual effect was attributed to allergy and indicated the danger that might result from this phenomenon. I have cited the above cases to emphasize the fact that insulin allergy may have serious import. Some of those cases had to have insulin and some method had to be devised whereby their sensitivity could be decreased.

### METHODS OF TREATMENT

In order to treat properly a case of allergy to commercial insulin, it must first be determined whether the allergy is to insulin itself or to some other protein in the commercial preparation. Thus testing with pure crystalline insulin will eliminate the possibility of the allergic reaction being due to the pancreatic tissue of the animal. Hughes<sup>12</sup> reported a case of urticaria following protamine zinc insulin and, after study, concluded that the sensitivity was to the protamine. Tuft<sup>17</sup> in his "Review of Insulin Hypersensitiveness" reported two cases; one due to allergy to an extraneous protein in the commercial preparation, and one that showed skin reactions both to crystalline insulin and to the commercial product. Where the allergy is proven to be due to other than the insulin factor, a change of product or the use of crystalline insulin will solve the problem. However, when the insulin factor is involved, then only one of two methods of treatment can be followed: either control of the diabetes by strict diet alone or an attempt at desensitization or hyposensitization. Various methods have been used in attempting to produce desensitization or hyposensitization; and histamine as well as insulin has been employed as the antigen.

Bayer<sup>2</sup> employed the rapid method of desensitization in his case starting at 9:15 a.m. and continuing until 5:20 p.m. During this time, seventeen intradermal injections ranging from .001 unit to 1 unit were given. An eighteenth injection consisting of 5 units was given hypodermically at 5:20 p.m. This patient was able to tolerate 10 to 15 units of insulin daily following this treatment, but within two weeks time urticarial reactions reappeared.

Corcoran's<sup>6</sup> patient could not be controlled on diet alone, and he treated his patient by the rapid method of desensitization beginning at 7:30 a.m. and continuing until 9:00 p.m. During this time a total of thirty injections were given at intervals varying from five minutes to forty minutes. Various routes of administration were used during the course of treat-

ment including intradermal, subcutaneous and intravenous. The highest intradermal dose was 4 units; the highest subcutaneous dose 40 units; and the highest intravenous dose 30 units. At the end of twenty-four hours the reactions to intracutaneous tests were entirely negative and following this the patient was able to tolerate 20 units of insulin daily.

Allen and Scherer<sup>1</sup> also used the rapid method on their patient following an operation for an empyema of the gall bladder. This patient postoperatively developed acidosis with a  $\text{CO}_2$  of 21.1 vol. per cent and a blood sugar of 295, and was in a critical condition. Treatment was begun with  $\frac{1}{4}$  unit of crystalline insulin. The injection was repeated at one-half hour intervals, increasing the dosage 50 per cent each time, unless the local reaction was too severe. At the end of six hours the patient was receiving 3 units. This dose was repeated hourly during the night. The following morning her  $\text{CO}_2$  was 64.5 vol. per cent. The patient's clinical condition improved and the dosage of the insulin was increased. Eventually, the patient was able to tolerate 40 to 50 units of crystalline insulin. Subsequently the patient was treated in a similar manner with commercial insulin. Improvement continued so, after two weeks, treatment was discontinued. Eleven days after treatment was discontinued skin tests were performed. There was an immediate local and generalized reaction manifested by local swelling, pruritis, and some swelling of the lips. Thus there had been a return of extreme hypersensitivity.

Slower methods of desensitization with insulin have been attempted. Herold<sup>11</sup> treated his patient by giving daily injections beginning with  $\frac{1}{250}$  unit and gradually increasing every day. After two months the patient was able to tolerate 24 units of insulin daily without any allergic reaction.

Bryce<sup>4</sup> reported a case which she desensitized, first, by daily and then by twice daily injections, beginning with minute amounts and increasing until the patient was able to take the needed amount twice a day.

Davidson<sup>7</sup> reported the case of a sixty-two year-old diabetic who developed severe urticaria following insulin injection. In addition to urticaria, it was also found that her diabetes was difficult to control even with increased dosage of insulin and rigid diet. Desensitization was carried out beginning with 1 unit and increasing by 1 unit every three or four days up to 8 units. Her blood sugar almost reached normal and her urine became sugar-free. The author, however, is not certain whether the desensitization procedure had any effect on the outcome of the case, since her reactions had almost completely disappeared before desensitization was instituted.

Methods other than the rapid and slow desensitization with insulin have been used. Thus, Kaufmann<sup>14</sup> described three cases of severe reaction to insulin which were relieved by one or two intracutaneous injections of from 4 to 6 units. Hughes<sup>12</sup> employed "Hapamine," four



weeks after treatment was instituted there still had been no return of urticaria. Collens, Lerner and Fialka<sup>5</sup>, failing to desensitize their patients by the slow method with insulin, employed histamine phosphate beginning with .1 mg. and gradually increasing until the patient was receiving 1.0 mg. per dose. Injections were given three times weekly for thirteen doses. Following the last injection of histamine the patient was able to tolerate 10 units of insulin daily; six months later he was taking 15 units of insulin daily without any reactions. Karr, Kreidler, Scull and Petty<sup>13</sup> sensitized a rabbit with gradually increasing doses of their patient's serum. This rabbit serum showed allergic antibodies when using insulin as the antigen. Some of this rabbit serum was then given to the patient. The patient demonstrated a fall in her insulin requirement and after about a month it was possible to discontinue insulin entirely. This last case tends to fit into the concept of hyposensitization by producing an abundance of free circulating antibodies which combine with the antigen and thus protect the living cells.<sup>21</sup> Urbach<sup>19</sup>, in discussing the treatment of insulin allergy, mentions, in addition to the slow and rapid methods of desensitization, the method of skeptophylactic de-allergization. In this procedure he recommends the administration of  $\frac{1}{2}$  to 1 unit of insulin subcutaneously forty-five minutes before the main injection. Urbach defines de-allergization as a process whereby antibodies are neutralized, and has demonstrated loss of sensitivity in the lung and uterus of experimental animals when employing this method, using food digests (propeptans).<sup>20</sup> The principle of this treatment is based on the demonstration by Besredka<sup>3</sup> that the pre-administration of a given antigen affords complete protection against what would otherwise be a fatal dose of allergen. According to Urbach, de-allergization differs from hyposensitization in that the latter is a method whereby clinical insensitivity is due to the production of an excess of free circulating antibodies by the repeated administration of small doses of antigen. In his treatment of food allergy Urbach employs food digests (propeptans) rather than the native protein maintaining that the degree of hypersensitiveness may be so high that even very small quantities of the particular food may produce anaphylactic symptoms. The food digest, on the other hand, will produce a state of anti-anaphylaxis by bringing on a microshock sufficient to neutralize temporarily the available supply of antibodies. The phenomenon of de-allergization is produced by following the administration of the specific propeptan by the native food protein. The neutralization of the antibodies that follows results in clinical insensitiveness.

In the case to be reported, due to the failure of other methods of desensitization, as will be described, treatment was carried out according to Urbach's method with some modifications. Hughes<sup>12</sup> recently reported a case of sensitivity to protamine insulin in which skeptophylactic de-allergization failed to occur. It was thought advisable, therefore, to try Urbach's method, with two modifications. Rather than use an arbitrary

dose of  $\frac{1}{2}$  to 1 unit of insulin, as the pre-administration dose, the dose was determined on the basis of the size of the wheal produced on intradermal testing. This course was suggested by Hansel's<sup>9</sup> method of co-seasonal treatment of hay fever. It was thought that if neutralization of antibodies was to be accomplished,  $\frac{1}{2}$  to 1 unit might be too great a dose for a micro-shock, since cases have been reported in which the initial dose of insulin for the desensitization had to be .0001 unit or less, in order to administer an amount which could be tolerated.<sup>10</sup> The dose of insulin selected, therefore, was the amount which produced a wheal approximately 15 mm. in diameter and in this particular case it was  $\frac{1}{200}$  unit. The second modification was to administer the small dose intradermally rather than subcutaneously. This also was suggested by Hansel's<sup>9</sup> method of co-seasonal treatment of hay fever, since a great similarity was believed to exist between the daily administration of insulin and the daily inhalation of pollen. It was also thought that if neutralization of antibodies did not occur, and if relief of symptoms would actually be due to an increase of circulating antibodies, the intradermal route was the best way to produce an excess of antibodies quickly.<sup>18</sup>

#### REPORT OF CASE

The patient, aged twenty-five years, was admitted to Walter Reed General Hospital on November 25, 1945, with a diagnosis of diabetes mellitus. The patient had been an airplane mechanic for three years before induction into the army in April, 1944. There was no familial history of diabetes and no personal or familial history of allergic disease. On July 2, 1945, he was hospitalized at a general hospital on Tinian Island because of severe abdominal pain and vomiting of twenty-four hours duration. He stated that he previously had been in apparently good health, but after careful questioning he admitted that, for about three months prior to his admission to the hospital, he had noted frequency of urination as well as polyuria, polydipsia and polyphagia, and a loss of about 40 pounds in weight. On routine examination of his urine a positive qualitative test for sugar was found and a subsequent fasting blood sugar was found to be above normal limits. Treatment was started with protamine zinc insulin, and about three weeks after treatment was instituted, he first noted that at the site of each injection he would develop a large indurative red reaction which persisted for twelve to fourteen hours and necessitated the application of hot compresses. Subsequently, he noted local urticaria in addition to the local reaction, and still later generalized urticarial reactions developed. Skin tests were performed overseas with insulin, and a positive reaction was found. It was recommended that he receive "desensitization treatments" after he was returned to the United States.

For three months after his return to the United States he was hospitalized at a general hospital and continued to receive insulin daily. Generalized urticaria developed after each injection. On arrival at Walter Reed General Hospital skin tests were performed using various insulin products. He had a marked reaction to regular insulin, "a less marked" reaction to one brand of protamine zinc insulin and globin insulin, and a slight reaction to another brand of protamine zinc insulin. Skin tests with beef and pork were negative. Rapid desensitization with protamine insulin was attempted by the intradermal route beginning with  $\frac{1}{1000}$  unit and increasing the dose at ten to twenty-minute intervals until 1 unit was reached. A total of ten injections were given. Urticaria following daily administration of

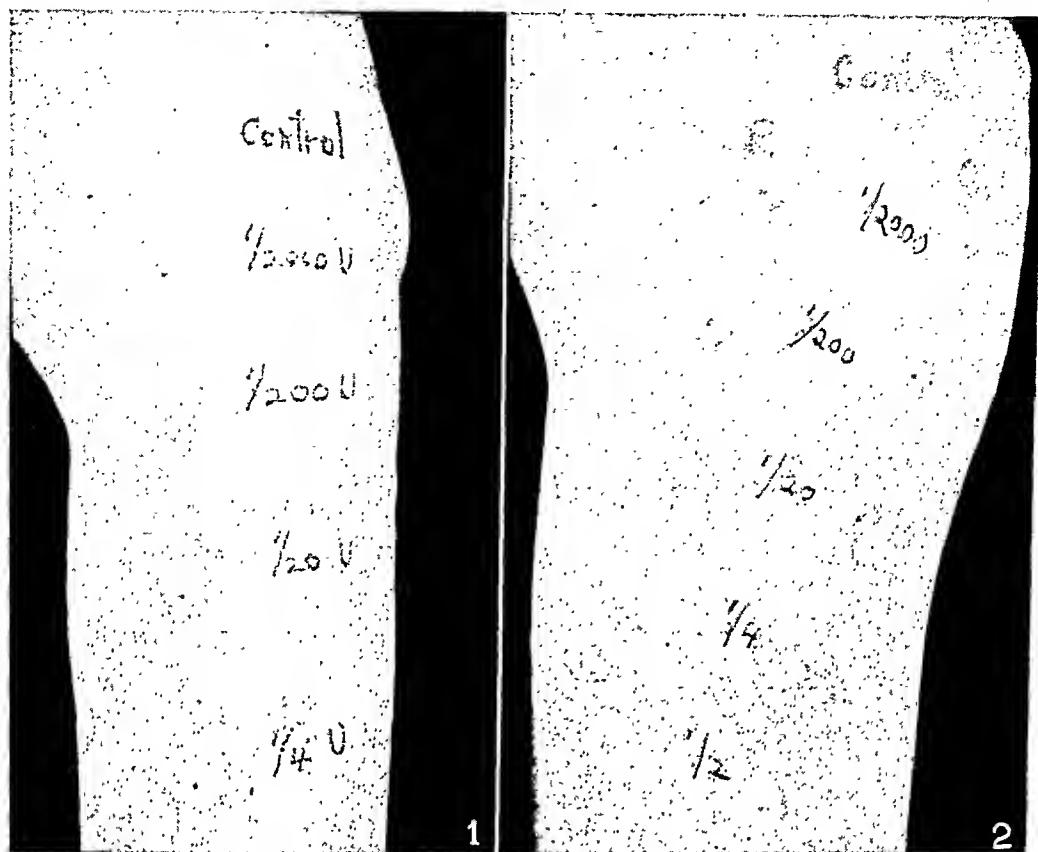


Fig. 1. Intradermal skin tests with varying doses of regular insulin. Each dose was contained in 0.05 c.c.

Fig. 2. Intradermal skin tests with varying doses of regular and crystalline insulin. R—regular insulin. C—crystalline insulin. Each dose was contained in 0.05 c.c.

25 units of globin insulin persisted. Subsequently desensitization with histamine was attempted but this also failed to alleviate the symptoms. The patient was placed on benadryl, 50 milligrams three times daily, and this gave him complete relief of his urticaria for three weeks, after which the urticaria returned and persisted in spite of the continued administration of benadryl.

On March 17, 1946, the patient was referred to allergy clinic for further study and recommendations. Skin tests with regular insulin were performed, and they revealed positive reactions beginning with 1/200 unit (Fig. 1). Passive transfer tests failed to reveal the presence of skin-sensitizing antibodies (reagins). The patient's ward officer was instructed not to give the patient any more insulin, and control of the diabetes was attempted on a strict dietary regime. In the meantime hyposensitization therapy was instituted on a bi-weekly schedule by the intradermal route. The first dose consisted of 1/1000 unit, the second, 2/1000 unit, repeated on three subsequent occasions, after which he received one dose of 1/200 unit. In all, he received six intradermal injections between March 25 and April 5, 1946. At that time his blood sugar was over 200 mg. per cent, he had lost weight, and therefore his ward officer insisted on resuming daily doses of insulin. Since hardly enough time had elapsed for desensitization or hyposensitization to have taken place, the possibility was considered of treating this patient by the skeptophylactic de-allergization method with the modifications described above. The ward nurse was instructed to give the patient 1/200 unit of regular insulin, intradermally, three-fourths to one hour before administering 20 units of globin

insulin. This form of therapy was instituted on April 6, 1946. On that day he had two- to three urticarial lesions for the first time since the insulin had been discontinued. After that he had no more urticarial lesions although he continued to receive 20 units of globin insulin daily, preceded by the 1/200 unit of regular insulin intradermally. He noted also a decrease in the size of the local reaction.

This form of therapy was continued until April 25 when the patient went on a three-day pass. He continued to take 20 units of globin insulin daily, but discontinued the intradermal dose. When he returned to the hospital he continued to take his daily insulin, increasing the dose to 25 units, but the intradermal dose of 1/200 unit was still omitted. The patient remained free of urticaria, although he did remark that there was an increase of erythema and induration at the site of the injection.

On May 1 skin tests were repeated using crystalline insulin in addition to regular insulin. The reactions to the regular insulin were essentially the same as they were on March 18. The reactions to crystalline insulin, although not as marked as to the regular insulin, were definitely positive beginning with 1/20 unit and markedly positive to 1/2 unit (Fig. 2).

On May 9 the patient began complaining of the appearance of one or two red blotches appearing in the late afternoon or evening and itching only very slightly. On May 13 there was a complete recurrence of the generalized urticaria. He was again placed on the program of receiving 1/200 unit of insulin intradermally three-fourths to one hour before his usual dose of insulin. Again he had a complete cessation of the generalized urticarial reactions. On May 17 the patient reported that he was receiving 25 units of globin insulin daily, and that so long as he received his intradermal dose at least three-fourths of an hour before his regular dose he would have no urticaria. However, on two occasions he had received his intradermal dose only ten minutes before his regular dose and, on both occasions, generalized urticaria resulted. Since his skin reaction to the 1/200 unit had decreased in size, the dose was increased to 1/100 unit, and the time interval was more carefully observed.

On May 21, 1946 the patient was ready to leave the hospital, having no urticarial reactions at all and such slight local reactions that he was conscious of no discomfort. He was instructed in giving himself the intradermal injections and requested to communicate with the clinic on his progress.

Just before the patient left, a blood specimen was drawn for the purpose of performing additional passive transfer tests. The same recipient was used as was on the first occasion and this time there was a questionable reaction to 1/2 unit of both regular and crystalline insulin. When another recipient was used there was a definite reaction to regular insulin and a slight reaction to crystalline insulin.

On June 17, 1946, a letter was received from the patient stating that he was well but beginning to develop a few "hives" during the evening. He stated that these urticarial lesions were not severe enough to cause him any discomfort. The patient was instructed to increase his morning intradermal dose of insulin to 1/50 unit and, if that failed to prevent the urticaria occurring in the evening, to revert back to the 1/100 unit intradermally in the morning followed by a second 1/100 unit intradermally in the early afternoon. The morning intradermal dose, of course, was to be followed by his regular dose of globin insulin whereas the afternoon intradermal dose was given alone.

On June 29, a second letter was received from the patient stating that he had increased the intradermal dose as directed and that, although he had continued this for ten days, he was still having a few "hives" in the evening. He further stated that he was beginning to "spill a little sugar in the evening." The patient said that he would now try the second suggestion and report further.

On July 17, patient again wrote that since his last letter he had been taking 1/100 unit of insulin intradermally, morning and afternoon, and that institution of this procedure had resulted in a complete cessation of the evening urticaria.

The above train of events is quite interesting since it so closely resembles the course often taken in the co-seasonal treatment of hay fever. The exposure to a prolonged action insulin product is also comparable to twenty-four hour exposure to atmospheric pollen.

#### DISCUSSION

This case has been presented primarily because it represents a slight departure from the usual methods of treatment of insulin allergy and with apparently good results. If this method proves to be equally successful in other cases, it would then offer a means of giving quick relief from very unpleasant reactions without the discontinuance of insulin administration. As to throwing more light on the immunologic principles involved, I am afraid that I have contributed nothing. The patient was definitely allergic to the insulin factor as proved by a positive reaction to crystalline insulin. Although no skin sensitizing antibodies (reagins) were demonstrated on the first passive transfer, they were demonstrated on the second attempt. It is interesting to note that there was a greater reaction on one recipient than on the other. The recipient, who showed the doubtful reaction on the second transfer, showed no reaction on the first and it is possible that we were dealing here with an individual whose skin was not receptive.<sup>16</sup> Because of this likelihood, it becomes impossible to attribute the appearance of a marked passive transfer reaction on a new recipient to an increase in circulating antibodies produced by the treatment. That a state of hyposensitization or refractoriness was produced, however, cannot be denied as evidenced by the relief of symptoms both at the beginning of treatment and at the resumption of treatment following the relapse when the intradermal doses had been discontinued. The mechanism involved in this state of refractoriness, however, is not clear. If skeptophylactic de-allergization occurred, then there was a neutralization of fixed antibodies but obviously not a permanent one. This fact however can neither be proven nor disproven. Vaughan,<sup>21</sup> in discussing the co-seasonal treatment of hay fever by small dose therapy, stated very definitely that the process was not one of antibody exhaustion, since skin tests and passive transfer tests indicated a persistence of reagins in the blood. However, in support of the possibility that the refractoriness may be due to saturation of tissue antibodies is the statement by Zinsser<sup>23</sup> that the fact that reactive antibodies appear free in the circulating blood does not preclude the possibility that fixed tissue antibodies have been neutralized. He further states that the neutralization of the fixed antibodies may actually result in a reaction whereby the living cell produces more antibodies and thus results in a superabundance of free antibodies or reagins in the blood. Ratner<sup>15</sup> states that the refractoriness of anti-anaphylaxis or desensitization may result

either from a partial or complete saturation of tissue antibodies with antigen or by the saturation of the blood with a large amount of circulating antibodies. According to Zinsser, however, both these reactions may occur simultaneously as part of the same mechanism. The relief offered by Karr et al<sup>13</sup> to their patient by the administration of sensitized rabbit serum appears definitely to have been due to the introduction of a large amount of circulating antibodies which prevented the antigen from reaching the fixed tissue antibodies.

To attempt to explain further the mechanism involved in the relief given this patient would purely be more conjecture with an admixture of a brand of "rocking chair philosophy." Harten and Walzer<sup>10</sup> aptly state that, in view of the fact that the mechanisms involved in the production of allergic reactions may differ in the various forms of insulin sensitivity, it would be foolhardy to attempt an explanation of the effect produced by specific treatment. Thus Tuft<sup>17</sup> in 1928 demonstrated that in addition to skin sensitizing antibodies (reagins), there were also present in some people allergic to insulin a precipitin antibody to insulin. Tuft also showed that in his case, reagin persisted after the precipitin antibodies had disappeared. In some cases, insulin allergy, like other types of acquired allergy, has been very transitory. All these facts merely indicate that further and more thorough immunologic studies must be carried out in the field of insulin allergy before the question of specific treatment can be intelligently undertaken.

#### SUMMARY

1. Although systemic allergic reactions to insulin are comparatively rare, they may occur with intensity severe enough to necessitate some form of specific treatment, particularly in those cases that cannot be controlled on a strict diet.

2. Various forms of treatment are reviewed, including slow and rapid desensitization with insulin, desensitization with histamine and hapamine, transference of specific antibodies from insulin-sensitized rabbit serum, and skeptophylactic de-allergization as described by Urbach.

3. A case of insulin allergy is reported which was completely relieved by a modification of Urbach's method of skeptophylactic de-allergization. The patient was given 1/200 unit of insulin intradermally three-fourths to one hour before the required dose of insulin. The intradermal dose was determined on the basis of the dose sufficient to produce a wheal approximately 15 mm. in diameter. This modification was suggested by Hansel's method of co-seasonal treatment of hay fever.

4. The mechanism of specific desensitization to insulin hypersensitivity is not clear, and further immunologic investigations are necessary before this phenomenon can be better explained.

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#### PURPURA INDUCED BY THE INITIAL INJECTION OF A PERTUSSIS VACCINE. P. Freud, and W. B. Greenberg. *Arch. Pediat.*, 63: 157-165, 1946.

The authors review the literature of reactions following the injection of pertussis vaccine and observe that purpura is rare and has in the past occurred only after repeated injections. They report the first case in which the initial injection of pertussis vaccine was followed by a generalized purpura.

The patient was a one-year-old negro male infant who was injected with 1 c.c. of the New York City Health Bureau pertussis vaccine (Mishulow). Twenty-four hours later a bright red petechial rash was noted involving the dorsum of the hands, the extremities and buttocks. The child was thought to have had fever preceding the appearance of the eruption. The child's personal and family histories were negative for allergy and his past history was otherwise non-contributory. An erythematous indurated area about the size of a penny was noted over the lateral aspect of the left deltoid muscle, the site of the injection. The right forearm, where no injection was given, was edematous with numerous petechiae. The Vollmer patch and Wassermann tests were negative. Blood studies were made, the most striking finding being a gradual reduction in platelets.

The child ran an uneventful course and was discharged after ten days. Five months later he was given 0.10 c.c. of the same pertussis vaccine intradermally,

(Continued on Page 224)

# EVALUATION OF INTRAMUSCULAR INJECTIONS OF SPECIFIC EXTRACTS IN THE TREATMENT OF ACUTE POISON IVY DERMATITIS

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SHOULD poison ivy extracts be used for the treatment of the acute dermatitis? In view of the high incidence of dermatitis from this plant, the answer to this question is of practical as well as of theoretical importance. It appears that it was Schamberg<sup>7</sup> who first popularized the oral use of an extract of *rhus toxicodendron* for the treatment of poison ivy dermatitis. He reported that tincture of *rhus toxicodendron* had a favorable influence in attacks of ivy poisoning in preventing an extension of the process and in abbreviating the duration of the attack. He maintained that no necessity for injections existed, because oral therapy was sufficiently satisfactory. Strickler<sup>12</sup>, commenting on the rationale of non-specific topical therapy in rhus dermatitis, said that the weakness of this mode of treatment is the attempt to overcome a specific inflammatory reaction with non-specific remedies. It occurred to him that the employment of the active principles derived from the plants, which had produced the dermatitis, represented the rational therapeutic method of procedure. Strickler reported that as a rule, to which there are few exceptions, within twenty-four hours after the first injection of an alcoholic solution of poison ivy extract, the itching associated with rhus dermatitis disappeared completely or was greatly modified. The skin was usually restored to normal in four to five days after treatment was instituted except in those generalized cases of dermatitis venenata in which the restoration of the skin to normal may be more delayed.

The Council on Pharmacy and Chemistry admitted rhus preparations to New and Non-Official Remedies in 1926.<sup>11</sup> This recognition was based chiefly on the favorable reports of Schamberg<sup>6,8</sup>, Strickler<sup>13,14</sup>, Alderson,<sup>1,2</sup> Bivings,<sup>3</sup> and Williams and MacGregor<sup>15,16</sup> that patients with rhus dermatitis were remarkably benefited by the administration of the extracts. It is important to remember that there were no control cases considered by these authors. The introduction of this measure was timely as it occurred in 1916-24, during the period when medical minds were constantly searching for a specific serum for infectious diseases and other disorders for which there were no specific chemotherapeutic remedies.

It was believed necessary to administer the specific extract of poison sumac, poison oak, or poison ivy depending on which plant allergen the patient contacted. Our present-day concept is that the same dermatitis-producing fraction is common to all three plants.

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Read by Dr. Rudolf Baer at the meeting of the American College of Allergists, San Francisco, California, June 28 to 30, 1946.



Since the favorable reports of Schamberg, Strickler, and others, the opinions concerning the therapeutic value of poison ivy extracts have been widely divergent. Thus for example Williams and MacGregor<sup>15,16</sup> considered that the method was an effective form of therapy while Pusey<sup>5</sup> and Morrow<sup>4</sup> denied that it had any beneficial effect. In order to shed further light on this problem Dr. Shelmire and I undertook the following series of controlled investigation.

#### A COMPARISON OF THE EFFECT OF INJECTIONS OF SPECIFIC AND NON-SPECIFIC SUBSTANCES ON THE COURSE OF IVY DERMATITIS

Forty patients with acute poison ivy dermatitis were studied. Their eruptions occurred during the spring and summer months and were seen in the private practice of Dr. Bedford Shelmire and myself. Twenty-three patients were given from one to four intramuscular injections of poison ivy extract (Lederle) during the course of their eruption. Seventeen patients were used as controls and were given from one to four injections of either crude liver extract or proteolac (Searle) intramuscularly or of strontium bromide intravenously. All patients were allowed to use starch bathing, wet dressings, an anti-pruritic shake lotion or emulsion for the symptomatic treatment of itching and burning. In each case efforts were made to discover accurately the number of days required for the "cure." The estimates were based chiefly on the period which elapsed before the disappearance of the rash and the subjective symptoms. The followup of the cases was difficult and necessitated keeping contact with the patient by phone, by correspondence and through frequent visits to the office for observation.

The patients who received the specific extract by injection were not able to sleep any better, did not have fewer cycles of pruritus, less discomfort or any appreciable benefit from injections given before or during the height of the reaction.

In both groups, an occasional patient stated that itching stopped for a few hours soon after receiving the injection. There was absolutely nothing that could be considered specific or strikingly beneficial from the use of poison ivy extract. In this connection it should be mentioned that Sharlit<sup>9</sup> and others have observed that injections of absolute alcohol subcutaneously in poison ivy dermatitis and in similar pruritic eruptions are often followed by a lessening of the subjective symptoms. Perhaps the improvement in Strickler's patients was due to the alcohol instead of the specific allergen of the rhus plant.

The untoward reactions that have been observed to follow the intramuscular administration of ivy preparations are erythema and induration of the area receiving the injection, accentuation of itching, urticaria, multiforme erythema, dyshidrosiform dermatitis of the hands, and marked brawny edema of the sites of the existing dermatitis. These reactions have been interpreted as a dermal combined with an epidermal reaction. In

patients who developed a hematogenous dermatitis due to the poison ivy extract it was my impression that the course of the eruption was appreciably lengthened and the discomfort accentuated.

In summary, no significant differences in the rate of healing could be

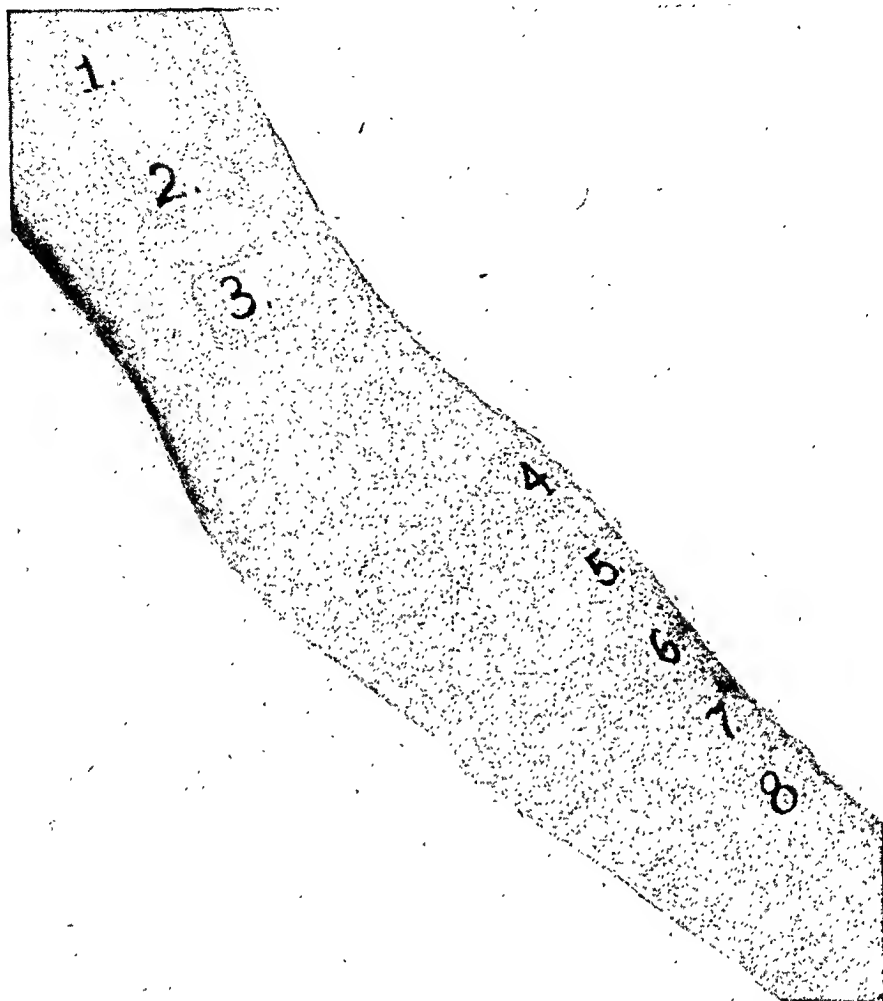


Fig. 1. Results of patch tests on author's arm with commercial poison ivy extracts. Only three brands were sufficiently potent to elicit a positive patch reaction.

noted in the two series and the course was never aborted even when the injections were given within the first forty-eight hours after exposure to the plant. Judging both the poison ivy injection series and the control series by the same clinical criteria for cure, the average time required per case was approximately thirteen days in both series.

#### DERMATITIS-PRODUCING POTENCY OF COMMERCIAL POISON IVY EXTRACTS

An interesting observation was made concerning the dermatitis-producing potency of commercially purchasable ivy preparations to be given intramuscularly or orally. Figure 1 demonstrates the astonishing fact that

despite the high degree of the author's poison ivy sensitivity only three of eight brands of ivy extract gave a positive patch reaction on the author's arm on one occasion. Repeating the same procedure on other occasions it was found that most of the commercial extracts produced feeble reactions when applied as patch tests on subjects highly allergic to the poison ivy plant. These results indicate purchasable poison ivy preparations vary widely in their potency to produce skin reactions and some contain an insufficient quantity of allergen to elicit a positive reaction even in highly sensitive subjects. This may explain why only a few patients are made worse by the injection of these extracts and, of course, the negligible quantity of dermatitis-producing agents might well render these ineffective in treatment, provided one accepts the thesis that specific therapeutic effect and specific skin reaction are due to the same allergenic constituents. It is, however, conceivable, though not yet proved, that therapeutic efficacy and production of skin reaction are not necessarily based on identical allergenic agents.

#### PRESENT STATUS OF SPECIFIC TREATMENT

Intramuscular injections of poison ivy extracts are in general use today chiefly because of the recommendation of this procedure by Strickler and the enthusiastic reception it received. The rationale for the use of specific allergens for treatment is based on the principle of specific hypsensitization. This principle may be applicable to certain infectious diseases. For example, vaccination with cowpox virus early in the course of smallpox is thought by some to abort or to favorably modify the disease.

However, Stevens<sup>11</sup> in an excellent summarizing review states that "the data offered in the literature are not convincing in regard to the phylactic value of treatment with antigens of ivy orally or parenterally." He states further that "many patients are made worse because severe reactions occur when large doses of extracted solids are injected, and since the practice is not in conformity with theory, it is believed that the treatment of acute ivy rashes either parenterally or orally with ivy extracts should be vigorously discouraged." Both Shelmire's<sup>10</sup> experiments and the present results tend to support these statements.

#### THE COURSE OF IVY DERMATITIS WHEN NO INJECTIONS OF SPECIFIC ALLERGENS ARE ADMINISTERED

Before giving credit to a therapeutic procedure, the natural course of ivy dermatitis without that measure must be understood and taken as a base line for comparison. We know that rhus dermatitis is a self-limited disorder of relatively short duration, and healing occurs without therapeutic assistance. Several basic factors appear to determine the course and duration in the individual case. One of these is an unknown, individual variability. Some people overcome contact dermatitis much more speedily than one anticipates (within a few days), while some persons consistently

require a lengthy period for healing (several weeks). Moreover, it can be shown that, experimentally, when large amounts of poison ivy oleoresin contact the skin, the resulting dermatitis is more intense and the course longer than when smaller amounts are used on the same individual. It is also established that the subjective symptoms are more distressing when larger areas of the skin surface are involved. Thus a patient may tolerate a few patches of dermatitis venenata but be most miserable when the dermatitis involves larger areas of the integument. If certain skin sites have repeatedly been the seat of rhus dermatitis, they may exhibit a higher degree of allergic response than other areas in the same individual and of course people vary widely in their degree of hypersensitivity to the rhus plants. Those who have acquired a high degree of allergic sensitivity to rhus usually respond to exposure with reaction of longer duration than those possessing lower degrees of sensitivity. In addition, the subjective reaction to rhus dermatitis depends on individual variations similar to the variation of pain tolerance. Lastly, the discomfort in ivy dermatitis is not continuous but comes in waves of varying severity or intensity and duration.

## SUMMARY

The present results in the employment of intramuscular injections of a potent brand of poison ivy extract (Lederle) in the treatment of acute poison ivy dermatitis did not confirm the claims of Strickler and others who introduced and popularized this procedure. The itching, burning and other discomfort did not disappear or become lessened in twenty-four to forty-eight hours following the first injection in any of the treated patients. When both series were appraised by the same clinical criteria for cure, the average time required for healing was the same in the group treated with ivy injections as in the control series.

Based on these results it is the author's opinion that poison ivy extract is contra-indicated for the treatment of acute rhus dermatitis. The procedure has not stood the test of time and has often been observed to do harm. The fundamental basis for phylactic therapy is unsound.

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## FOOD ALLERGY IN DOGS

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**S**UPERSENSITIVITY to food has been demonstrated in dogs affected with eczema.<sup>1,4,5</sup> Also the allergic origin of angioneurotic edema, due to foods, was ascertained as early as 1922.<sup>3</sup> In my practice, eight cases have been observed in dogs where food allergy could be established as the cause of serious disease.

Three of these cases concern urticaria. In two of these, eggs could be ascertained as the causative agent by elimination experiments. In the third dog, the supersensitivity was caused by commercial baked dog food (kibbles).

In addition, five cases of hemorrhagic colitis were seen, one of them lethal. One of the cases was complicated by chronic eczema. Clinical cure could be obtained in three cases by elimination of horse meat from the diet, and a fourth one by that of kibble. The fifth animal died before the materia peccans could be ascertained. This animal was fed on beef and kibbles. The post-mortem studies of this dog showed acute colitis with hemorrhage and thrombosis of underlying blood vessels.

Six out of eight animals involved were pure bred.

As several of the animals affected with hemorrhagic colitis showed infestation with intestinal parasites, it may be worth while investigating<sup>5</sup> whether parasites may have something to do with making the intestinal wall more permeable for antigens.

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This is an abstract of a paper read at the annual meeting of the American College of Allergists, San Francisco, California, 1946. A more detailed account will appear in a veterinary journal.

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(Continued from Page 218)

and a wheal about 1.5 inches in diameter with pseudopods appeared at the site of the injection. Seven months later a similar test also resulted in a wheal. Subcutaneous injection of 1 c.c. of the vaccine resulted in local redness and induration and a rectal temperature of 100.4° F. Two days later 2 c.c. of the vaccine was injected and this was followed by reddening and induration for twelve hours. None of the intradermal or subcutaneous injections reproduced the purpura which was observed following the initial injection of the vaccine. The authors discuss the reasons for excluding thrombocytopenia as the mechanism for the purpura in this case and believe that the only explanation for the hemorrhagic tendency here appears to be capillary damage due to the liberation of histamine-like substances which are known to increase vascular permeability in shock and other anaphylactic conditions. They state that it is not surprising that purpura could not be reproduced by repeated injections of the vaccine, for rarely does anaphylactoid purpura recur in the same patient. Twenty other children inoculated with pertussis vaccine from the same lot as the reported patient in no instance developed purpura or any other anaphylactoid manifestation.

# THE CHEMICAL AND IMMUNOLOGIC BASIS OF ORAL POLLEN PROPEPTAN THERAPY IN HAY FEVER

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*(Continued from March-April issue.)*

*Experiment 4.*—Guinea pigs were allergized to dwarf ragweed pollen by subcutaneous injection of 5 per cent dwarf ragweed pollen extract precipitated with one per cent alum. Forty-five days later the following treatment was instituted.

Treatment: Five intravenous injections of dwarf ragweed digest at ten-minute intervals:

- Injection 1.—Pollen digest representing 1.0 mg. soluble nitrogen—No reaction.
- Injection 2.—Pollen digest representing 2.5 mg. soluble nitrogen—No reaction.
- Injection 3.—Pollen digest representing 5.0 mg. soluble nitrogen—Bristling.
- Injection 4.—Pollen digest representing 10.0 mg. soluble nitrogen—Bristling.
- Injection 5.—Pollen digest representing 20.0 mg. soluble nitrogen—Bristling.

Two hours later: Inhalation of shock dose of five per cent dwarf ragweed pollen for twenty minutes:

Reaction: Slight diaphragmatic breathing.

Animals killed two hours after bronchial shock dose:

Schultz-Dale test—Positive.

Lung perfusion test—Very weakly positive.

Animals which were killed six hours after the bronchial shock dose exhibited negative Schultz-Dale test and negative lung perfusion test.

Experiment 4 demonstrates that skeptophylactic intravenous injections of pollen propeptan afford effective protection against bronchial shock dose.

*Experiment 5.*—Guinea pigs were allergized to dwarf ragweed pollen by subcutaneous injection of 2.0 c.c. of 5 per cent dwarf ragweed pollen extract, precipitated with 1 per cent alum. Fifty-five days later the following treatment was instituted.

Treatment: Inhalation with 10 per cent dwarf ragweed digest for thirty minutes—No reaction.

Two hours later: Intravenous shock dose of 5 per cent dwarf ragweed pollen extract:

- Injection 1.—1 M.L.D.—No reaction.
- Injection 2.—2.5 M.L.D.—Bristling.
- Injection 3.—5 M.L.D.—Bristling and diaphragmatic breathing.
- Injection 4.—10 M.L.D.—Bristling.
- Injection 5.—20 M.L.D.—Bristling.

Animal killed two hours after last shock dose:

Schultz-Dale—Negative (Fig. 8).

Lung perfusion test—Negative (Fig. 9).

Experiment 5 shows that inhalation of ragweed propeptan for thirty minutes de-allergizes the entire organism of a highly sensitized animal to such a point that it can tolerate twenty M.L.D. by the intravenous route. De-allergization is demonstrated by the negative Schultz-Dale and lung perfusion tests (Figs. 8 and 9).

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*Experiment 6.*—Guinea pigs were allergized to dwarf ragweed pollen by subcutaneous injection of 2.0 c.c. of 5 per cent dwarf ragweed extract precipitated with 1 per cent alum. Fifty-five days later the following treatment was instituted.

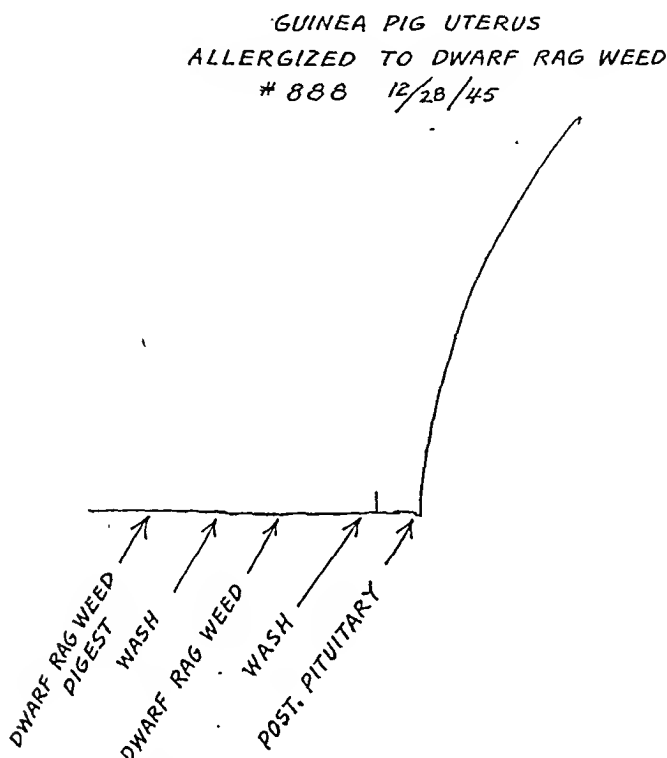


Fig. 8. Schultz-Dale test performed upon the uterus of a guinea pig allergized to dwarf ragweed pollen by subcutaneous injection of dwarf ragweed pollen extract precipitated with alum. Following a treatment of inhalation of dwarf ragweed pollen digest (dwarf ragweed pollen propeptan), the animal was able to tolerate a twenty times minimal lethal intravenous shock dose of dwarf ragweed pollen extract. The animal was killed two hours after the last injection. There was no reaction upon the addition of dwarf ragweed pollen digest or dwarf ragweed pollen extract, indicating the absence of antibodies.

Treatment: Inhalation of 10 per cent dwarf ragweed digest for thirty minutes—No reaction.

Two hours later: Shock inhalation dose of 5 per cent dwarf ragweed, exposure for thirty minutes—Slight bristling and diaphragmatic breathing.

Two hours later: Animal killed:

Schultz-Dale test—Positive.

Lung perfusion test—Negative.

Animals killed six hours after shock inhalation dose showed the same results, i.e., positive Schultz-Dale and negative lung perfusion tests.

Experiment 6 shows that inhalation of ragweed propeptan protects highly allergized guinea pigs against bronchial shock dose. However, while the bronchial antibodies are neutralized (satiated), those of the uterus are not.

*Experiment 7.*—Guinea pigs were allergized to dwarf ragweed pollen by subcutaneous injection of 2.0 c.c. of 5 per cent dwarf ragweed pollen extract precipitated with 1 per cent alum. Fifty days later the following treatment was instituted.

Treatment: By mouth, 5 mg. of soluble nitrogen of dwarf ragweed propeptan plus 0.2 gm. of glycyrrhiza plus 2.0 c.c. of water.

Forty-eight hours later: Intravenous shock doses of dwarf ragweed pollen at five-minute intervals:

- Shock dose 1.—1 M.L.D.—No reaction.
- Shock dose 2.—2.5 M.L.D.—No reaction.
- Shock dose 3.—5 M.L.D.—No reaction.
- Shock dose 4.—10 M.L.D.—No reaction.
- Shock dose 5.—20 M.L.D.—Slight reaction, bristling.

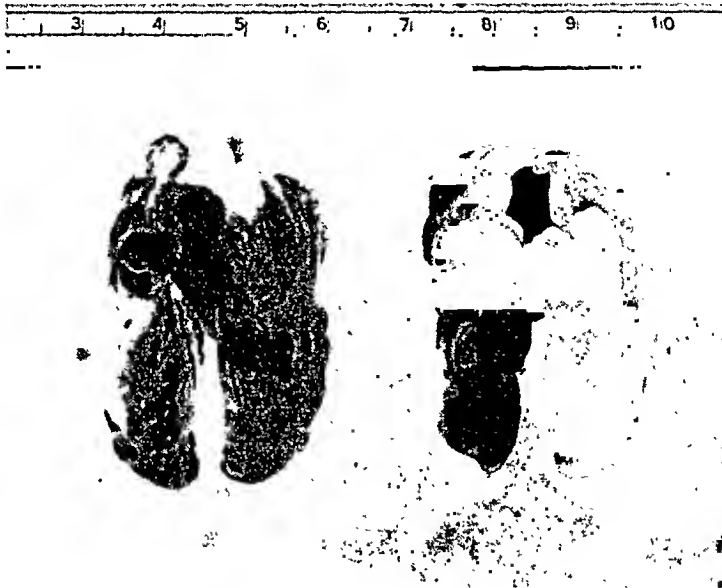


Fig. 9. Lung perfusion test performed upon the lung of a guinea pig allergized to dwarf ragweed pollen by subcutaneous injection of dwarf ragweed pollen extract precipitated with alum. Following a treatment of inhalation of dwarf ragweed pollen digest (dwarf ragweed pollen propeptan), the animal was able to tolerate a twenty times minimal lethal intravenous shock dose of dwarf ragweed pollen extract. The animal was killed two hours after the last injection. The lung (left) showed no inflation, indicating the absence of antibodies. A control lung of a non-allergized animal of the same weight (right) showed a negative reaction in the lung perfusion test.

Animal killed two hours after last shock dose by blow on the head:  
 Schultz-Dale test—Negative.  
 Lung perfusion test—Positive.

In animals killed six hours after last shock dose, both tests were negative. In those killed twelve hours after last shock dose the Schultz-Dale test was negative, but the lung perfusion test positive. When animals were killed twenty-four hours after last shock dose, both the Schultz-Dale test and the lung perfusion test were positive. However, in about 30 per cent of these experiments the guinea pigs would tolerate only ten M.L.D. and some animals exhibited marked diaphragmatic breathing even when receiving five M.L.D.

Experiment 7 demonstrates that oral administration of pollen propeptan protects only a fair percentage of animals against twenty M.L.D. of the antigen. However, in those cases where satisfactory protection was achieved, both uterus and lung were found to be free of antibodies six hours after administration of the last shock dose.

*Experiment 8.*—Guinea pigs were allergized to dwarf ragweed pollen by subcutaneous injections of 2.0 c.c. of 5 per cent dwarf ragweed extract precipitated with 1 per cent alum. Forty-six days later the following treatment was instituted.

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Treatment: Oral administration of 20 mg. of soluble nitrogen of dwarf ragweed digest plus 0.2 gm of glycyrrhiza plus 2.0 c.c. of water.

Sixty-six hours later: Inhalation shock dose of dwarf ragweed pollen, 5 per cent for thirty minutes—Bristling and diaphragmatic breathing.

Twenty-four hours later: Oral administration of 20 mg. of soluble nitrogen of dwarf ragweed digest, glycyrrhiza and water.

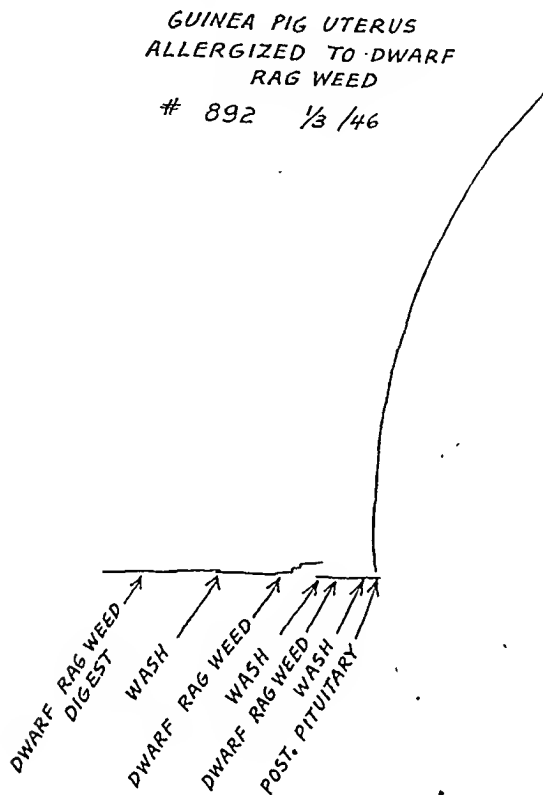


Fig. 10. Schultz-Dale test performed upon the uterus of a guinea pig allergized to dwarf ragweed pollen by subcutaneous injection of dwarf ragweed pollen extract precipitated with alum. The animal was treated with a series of oral administrations of dwarf ragweed pollen digest (dwarf ragweed pollen propeptan), followed by bronchial exposure to a pollen shock dose. The animal tolerated a ten times minimal lethal intravenous shock dose of pollen extract given two hours after the last inhalation shock dose. The animal was killed immediately after the intravenous shock dose. There was no reaction to dwarf ragweed pollen digest or dwarf ragweed pollen extract, indicating the absence of antibodies.

After two hours: Inhalation shock dose of dwarf ragweed pollen 5 per cent for thirty minutes—Bristling and diaphragmatic breathing.

Twenty-four hours later: (Same as previous twenty-four hours).

Twenty-four hours later: (Same as previous twenty-four hours).

Two hours after the last inhalation shock dose: Animal killed;

Schultz-Dale test—Negative.

Lung perfusion test—Negative.

If the animals were killed after six hours, the Schultz-Dale test was positive, the lung perfusion test negative.

Experiment 8 shows that temporary de-allergization is achieved (negative Schultz-Dale and lung perfusion tests), when oral administration of pollen propeptan is followed by bronchial exposure to a pollen shock dose, and the procedure is repeated three times at twenty-four-hour intervals.

*Experiment 9.*—Same procedure as in Experiment 8 except that an intravenous shock dose of dwarf ragweed pollen was given two hours after the last inhalation shock dose.

Shock dose 1.—2.5 M.L.D.—No apparent reaction.

Shock dose 2.—5 M.L.D.—No apparent reaction.

Shock dose 3.—10 M.L.D.—Very little bristling.

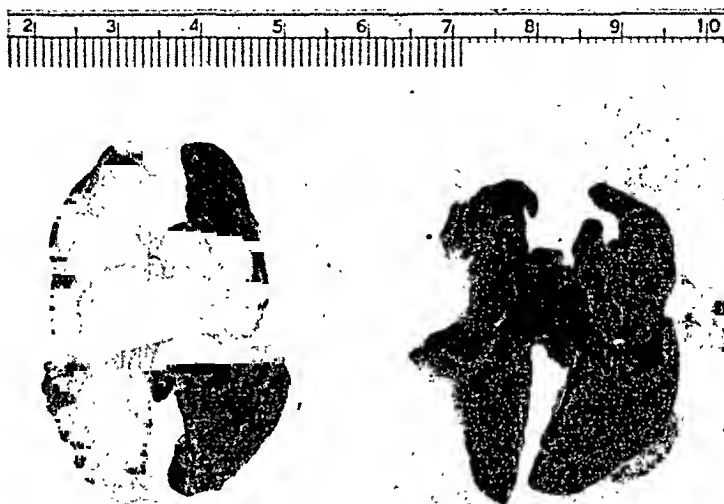


Fig. 11. Lung perfusion test performed upon the lung of a guinea pig allergized to dwarf ragweed pollen by subcutaneous injection of dwarf ragweed pollen extract precipitated with alum. The animal was treated with a series of oral administrations of dwarf ragweed pollen digest (dwarf ragweed pollen propeptan), followed by bronchial exposure to a pollen shock dose. The animal tolerated a ten times minimal lethal shock dose of pollen extract given two hours after the last inhalation shock dose. The animal was killed immediately after the intravenous shock dose. The lung (left) showed no inflation, indicating the absence of antibodies. A control lung of a non-allergized animal of the same weight (right) showed a negative reaction in the lung perfusion test.

Animal killed immediately after the last intravenous shock dose:

Schultz-Dale test—Almost negative (Fig. 10).

Lung perfusion test—Slightly positive (Fig. 11).

However, when six hours after the last inhalation shock dose 2.5 M.L.D. were given intravenously, the animal presented diaphragmatic breathing, and died in twelve minutes when ten M.L.D. were injected. The Schultz-Dale test was positive and lung was inflated.

Experiment 9 demonstrates that animals treated with pollen propeptans by the oral route and followed by bronchial exposure to pollen are given temporary protection against ten M.L.D., administered intravenously.

*Experiment 10.*—Guinea pigs were allergized to dwarf ragweed pollen extract precipitated with 1 per cent alum. Fifty-three days later the following treatment was instituted.

Treatment: Skeptophylatic inhalation of 5 per cent dwarf ragweed pollen extract 5 per cent as follows:

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- 10-28-45—10 a.m. Time of exposure, 30 seconds—No reaction.  
10-28-45—4 p.m. Time of exposure, 60 seconds—No reaction.  
10-29-45—10 a.m. Time of exposure, 1.5 minutes—No reaction.  
10-29-45—4 p.m. Time of exposure, 3 minutes—Bristling and diaphragmatic breathing.  
10-30-45—8 a.m. Time of exposure, 3.5 minutes—Bristling and diaphragmatic breathing.  
10-30-45—2 p.m. Time of exposure, 5 minutes—Bristling and diaphragmatic breathing.

Inhalation shock dose of dwarf ragweed pollen:

- 10-30-45—4 p.m. Time of exposure, 30 minutes—10 per cent dwarf ragweed pollen extract.

Reaction: Bristling and marked diaphragmatic breathing. Two hours after the bronchial shock dose the animal was killed. Schultz-Dale test—positive. Lung perfusion test—strongly positive.

If animals of this group were sacrificed six hours after the bronchial shock dose, the Schultz-Dale test was again positive but the lung perfusion test negative.

Experiment 10 demonstrates that skeptophylactic bronchial exposure to whole pollen gives moderate protection against bronchial pollen shock dose, satiating temporarily the bronchial antibodies but not those of the uterus.

*Experiment 11.*—Guinea pigs were allergized to dwarf ragweed pollen by subcutaneous injection of 5 per cent dwarf ragweed extract precipitated with 1 per cent alum. Forty-seven days later the following treatment was instituted.

Treatment: Oral administration of 5.0 mg. of soluble nitrogen of dwarf ragweed pollen and 7.5 c.c. of water and 0.02 gm. of glycyrrhiza, daily for three consecutive days. No reaction to oral administration of pollen.

Two hours after the last oral treatment: An inhalation shock dose of dwarf ragweed pollen extract 10 per cent for ten minutes. Moderate reaction, bristling and diaphragmatic breathing.

Animal killed two hours after shock dose:

Schultz-Dale test—Positive.

Lung perfusion test—Strongly inflated.

Experiment 11 shows that whole pollen of dwarf ragweed administered orally gives a moderate degree of protection against a bronchial shock dose.

*Experiment 12.*—Guinea pigs were allergized to dwarf ragweed pollen extract by subcutaneous injection of 2 c.c. of 5 per cent pollen extract precipitated with 1 per cent alum. Fifty days later the following treatment was instituted.

Treatment: By mouth, 5 mg. of soluble nitrogen of cocklebur digest, 0.2 gm. of glycyrrhiza plus 2 c.c. of water.

After forty-eight hours: Shock doses of dwarf ragweed pollen, 5 per cent extract, intravenously:

Shock dose—1 M.L.D.—Animal died in six minutes with asthmatic symptoms.

Schultz-Dale test—Positive.

Lung perfusion test—Positive.

Experiment 12 demonstrates that nonspecific pollen propeptans do not protect sensitized animals at all.

### DISCUSSION

Guinea pigs can always be strongly allergized by a subcutaneous injection of 2 c.c. of an aqueous extract of pollen precipitated with alum. This mixture insures slow absorption of the antigen. Sensitization is achieved somewhere between the forty-fifth and fifty-fifth day, provided the animal be kept on an acid diet.

Anaphylactic death will invariably follow intravenous administration of the shock dose. When the shock dose is administered by the bronchial route (in a specially constructed inhalation chamber), the overwhelming majority of animals will exhibit severe or deadly manifestations of anaphylaxis.

We also succeeded in allergizing guinea pigs by the bronchial route, whereupon these animals presented typical symptoms of bronchial asthma but no outright manifestations of anaphylaxis. In other words, we were able to induce the same symptoms in experimental animals as we so commonly encounter in human beings. This again refutes the very foundation of the concept of atopy which claims that "atopic" diseases, such as asthma, can occur only in human beings which are subject to hereditary influences. These experiments are more fully discussed in a separate paper.<sup>8</sup>

Group A comprises Experiments 3 and 4, in which highly sensitized animals were protected against twenty minimal lethal doses of pollen by skeptophylactic intravenous administration of pollen propeptans, i.e., by mounting doses of pollen digest given five times at ten-minute intervals. The fact that both the Schultz-Dale and the lung perfusion tests were negative indicates that the protection is attributable to neutralization (satiation) of the cellular antibodies. We call this form of immunologic protection "de-allergization," in contradistinction to "hyposensitization," in which both the cellular and the humoral antibodies are greatly increased in number (Urbach and Gottlieb<sup>5</sup>).

When the shock dose was administered intravenously, both the Schultz-Dale and the lung perfusion tests were negative two hours after the shock dose; however, when the animals were exposed to the latter by the bronchial route, it took six hours for the cellular antibodies in both the uterus and lung to be neutralized. This may be explained by the fact that, in the latter instance, it takes a longer time for the antigen to come into contact with the cellular antibodies.

In Group B (Experiments 5 and 6), treatment consisted of exposure to 10 per cent ragweed propeptan for thirty minutes in the inhalation chamber. The animals were able to withstand twenty M.L.D., injected intravenously, and the Schultz-Dale and lung perfusion tests were negative. Bronchial exposure to the shock dose was tolerated by the animals, but even after six hours the Schultz-Dale test was positive, indicating that not enough antigen had been absorbed to neutralize the antibodies of the distant shock organ. This, as we shall see below (Group C), differs from the findings in experiments where the antigen is given by mouth.

In Group C (experiments 7 and 8) the animals received pollen propeptan by mouth for protective purposes. Here again the vast majority was able to tolerate ten to twenty M.L.D. After two hours the Schultz-Dale test was negative, the lung perfusion test positive. After six hours both tests were negative. Twelve hours after administration of the multiple

minimal lethal dose, conditions were the same as those prevailing after two hours. After twenty-four hours both tests were positive. Oral administration of pollen propeptan, followed by bronchial exposure to the shock dose, repeated three times at twenty-four hour intervals, resulted in temporary de-allergization for the first two hours; after six hours the Schultz-Dale test became positive.

Why animals receiving pollen propeptan orally should, at first and then again later, give a positive lung perfusion test may perhaps best be explained by the fact that the lung contains a relatively greater number of antibodies, and that these are consequently more difficult to neutralize than those of the uterus.

Animals (Experiment 9) which were given pollen propeptan orally, and which then received a bronchial shock dose and lastly (two hours later) an intravenous injection of ten M.L.D. of pollen tolerated the latter almost without symptoms. At the same time the cellular antibodies in the uterus and lung were neutralized, as evidenced by the negative Schultz-Dale and lung perfusion tests. However, when the intravenous dose was administered six hours after the bronchial shock dose, all the animals died in anaphylactic shock.

In Group D (Experiment 10) the animals were treated with pollen extract instead of pollen digest. In Experiment 10 we subjected the animals to skeptophylactic inhalation of pollen extract, beginning with thirty seconds and gradually increasing the exposure to five minutes. While the animals withstood ten minutes of pollen inhalation, the Schultz-Dale test and the lung perfusion test were both positive. When treatment was begun with a three-minute exposure, the animals exhibited extremely severe symptoms of anaphylaxis in response to a five-minute inhalation period which followed the first exposure after a brief interval.

Oral administration of the whole pollen (Group E, Experiment 11) was found to provide a fair therapeutic result, but here again the reactivity of uterus and lung was strongly positive.

In Group F we endeavored to determine whether animals allergized to ragweed pollen could be protected by nonspecific pollen propeptan, e.g., cocklebur pollen propeptan. Without exception, these animals died following the first minimal lethal dose.

Lastly we should like to state that similar extensive experiments as with dwarf ragweed propeptan were made with cocklebur propeptan and timothy propeptan. Since the results were virtually identical with those observed in the series of experiments with ragweed pollen propeptan, we feel that they do not warrant detailed discussion.

#### SUMMARY

Pollen propeptans are pollen digests derived from the individual pollen through prolonged acid and alkaline digestion of the ragweed pollen group, and prolonged acid digestion of the grass pollen. While these preparations

are devoid of native protein, they do retain type-specific immunologic properties, as demonstrated by the positive passive transfer test (Prausnitz-Kuestner reaction) when pollen propeptan is substituted for the pollen proper.

In the extensive series of animal experiments, it was learned that grass pollen propeptans are most efficacious when the preparations contain some 80 per cent of proteoses and peptones. Ragweed and cocklebur propeptans, on the other hand, afford the maximal protection when these degradation components comprise no more than 50 to 55 per cent of the total preparation.

Intravenous, oral and bronchial administration of pollen propeptans, under appropriate conditions as to quantity and timing, can protect highly sensitized guinea pigs against as many as twenty minimal lethal doses. On the strength of the temporarily negative Schultz-Dale and lung perfusion tests exhibited by animals protected in this manner, the opinion is expressed that pollen propeptan therapy produces temporary neutralization of cellular antibodies, or, in other words, de-allergization rather than hyposensitization.

While administration of pollen propeptan causes at least a temporary de-allergization, that of whole pollen does not diminish the allergic reactivity of the chief shock organs, uterus and lung, as demonstrated by positive Schultz-Dale and lung perfusion tests.

The results of these investigations seem to constitute experimental confirmation of the therapeutic value of specific pollen propeptan therapy in hay fever in man.

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## ASTHMA DUE TO ODOR OF URINE, FECES AND SWEAT

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THE fact that asthma may result from the odor of food is well known. Feinberg and Aries<sup>1</sup> reported three cases of asthma from food odors. These attacks were caused by the odor of cooking foods. Horesh<sup>2</sup> described a case of a child in which the odor of white potato uncooked was responsible for such attacks. Ingested foods are known to produce asthma.

The literature seems to show no record of this affection caused by the end products of metabolism when excreted in the urine, feces or sweat.

For that reason the following case is of interest.

### CASE RECORD

A twenty-seven-year-old housewife complained that ever since returning from the hospital with her first baby, bottle-fed and at present four months old, she got attacks of wheezing and coughing every time she changed the wet diapers or when she washed them. These attacks came on in about two minutes and lasted for half an hour. Should the baby have a stool as well, the attacks were more severe. The information was also elicited that if there was passage of gas without urine or stool, she also had dyspnea, coughing and wheezing. As the history unfolded, it was learned that the smell of heavy perspiration gave similar distress. Aside from these causes, Limberger cheese or green cheeses produced a tightening in the chest with wheezing if they were on the table near her. Two other substances bothered her, the odor of rotting seaweed and the putrid smell of skunk cabbage.

As far as she knew, there was no allergy in the family.

Physical examination revealed no abnormality except on the numerous occasions when various substances were being tested. Then dyspnea was occasioned and rhonchi were present in the chest.

The possibility of baby powder, soap and the various articles used in the care of the baby was considered, but the usual tests eliminated them. On a visit to her home, the sniffing of dry diaper caused no trouble, but a wet diaper brought on a typical paroxysm. The urine was acid to litmus and there was no odor of ammonia.

The natural conclusion seemed to be that the aromatic or ethereal sulphates were responsible. These are some of the end-products of protein metabolism. A brief note on them is of importance. Sampson Wright<sup>3</sup> says:

"Some of the aromatic amino acids (tryptophane, tyrosine and phenylalanine) pass into the large intestine, where they undergo putrefactive change and are converted into indol, skatol and phenol. These substances are absorbed into the blood, carried to the liver, oxidized to indoxyl and

skatoxyl, conjugated with sulphate, and excreted in the urine as the so-called ethereal sulphate."

The patient was given test tubes containing the following separately: butyric acid, propionic acid, indol and valeric acid. On separate occasions she inhaled the odors of each.

Typical attacks were produced by all but valeric acid. Skatol was next tested and gave the most severe and prolonged attack.

Fresh urine was shaken up with an equal amount of ether and separated. This was repeated three times. The urine so treated failed to cause any trouble.

Folin states that on a protein-rich diet of adequate caloric value, the amount of ethereal sulphate excreted in the urine is 0.19 gm., whereas on a similar adequate but protein-poor diet, the amount of ethereal sulphate is only 0.1 gm.

In view of this fact, fresh urine from a patient on a protein-poor diet was given to the patient to inhale. She complained of only a slight feeling of tightness in the chest.

An investigation of the effect of perspiration was carried out next.

Sampson Wright<sup>3</sup> states that there are two kinds of sweat glands in man:

"1. *Eccrine*, which are distributed over the body surface and secrete a dilute solution containing sodium chloride, urea and lactate (in exercise). Eccrine glands are most dense on the palms and soles, next on the head, and much less on the trunk and extremities.

"2. *Apocrine*, large glands found mainly in the axilla and round the nipples, and in the female on the labia majora and mons pubis. They form a secretion of variable composition and characteristic odor."

Howell says that there are present in this sweat ethereal sulphates of phenol and skatol.

Sweat was collected from the face and upper chest and from the axilla separately. The former was clear and with little odor. The latter was cloudy and had a heavy smell.

The patient was allowed to inhale from the test tube containing the sweat which was mostly from the chin. There was no reaction. When the axillary sweat was tried, a typical attack with dyspnea, coughing and wheezing occurred, and rhonchi were present on stethoscopic examination.

#### SUMMARY

A case of asthma is reported which was due to the ethereal sulphates, the aromatic end products of protein metabolism as excreted in the urine, feces and sweat. The attacks due to cheese were no doubt caused by the acid formed by the propionic bacteria present in these foods.

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# REAGINS: PRELIMINARY REPORT ON EXPERIMENTAL EVIDENCE IN SUPPORT OF A NEW THEORY OF THEIR NATURE

## Immunochemical Studies of Reagin I.

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EVER since the publication of Prausnitz and Küstner<sup>9</sup> on local passive transfer in 1921 there has been general acceptance of the theory that some sort of antibody, now called reagin, is probably responsible for allergic reactions. Much speculation as to the immunological and chemical nature of reagin has followed.

Experimental work such as that of Coca and Grove<sup>2</sup> and of Loveless<sup>5</sup> has given us a good knowledge of the differences in properties between reagin and normal antibody. Thus we know that reagin as opposed to normal antibody seems to be more heat labile; that the ability to produce reagin appears to be inherited; that this does not preclude the ability in allergic individuals to produce normal antibody to the same specific antigen; that the duration of sensitization produced by reagin is relatively long; that reagin does not produce a precipitate with its specific antigen; that it sensitizes the human skin; and that it does not neutralize its specific antigen. All these differences lead to the speculation that reagin must differ chemically or physically from normal antibody.

Having these differences in mind, the authors have postulated that the production of reagin in the so-called allergic group of humans is the result of some hereditary factor which permits the individual to form incomplete or distorted antibodies, and that this process is probably due to some genetic lack or mutant analogous to that demonstrated by Beadle<sup>1</sup> as responsible for distorting or abbreviating the chain enzyme reactions in amino acid metabolism in the red bread mold (*neurospora crassa*).

Furthermore, it was postulated that since reagin cannot produce precipitate with its specific antigen it probably lacks sufficient combining groups to build up a lattice of antigen and antibody in conformity with Marrack's<sup>6</sup> "Lattice Theory." In the light of Pauling's<sup>8</sup> theory that a minimum of two combining groups on an antibody is necessary to build up such a lattice and that normal antibody probably has but two such groups, it was further postulated that reagin is probably an antibody with only one combining group, that is, a unipolar antibody.

The present investigation was undertaken to determine if by serologic

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This study was supported by funds provided by Mr. Harry Leveson through the Wescar Investment Company.

Read before the American College of Allergists, San Francisco, California, June 28 to 30, 1946.

TABLE I. HYPERSENSITIVE REACTIONS TO EGG WHITE OF PERSONS FROM WHOM TEST SERUMS WERE OBTAINED.

Patient	Symptomatic	Skin Tests	Prausnitz-Küstner
D	Negative ?	3-plus	Plus—minus
G	Positive	Minus	Plus—minus
Z	Positive	4-plus	4-plus
S	Positive	4-plus	4-plus
Se	Positive ?	3-plus	Minus
H	Positive	4-plus	4-plus
A	Negative ?	4-plus	4-plus
Y	Negative ?	3-plus	Minus
Sa	Negative	Minus	Minus

means some confirmatory evidence might be obtained for this theory. Using the precipitative reaction between ovalbumin and rabbit antiovalbumin, experiments were set up to determine whether reagin from egg-sensitive individuals would produce quantitative effects on the amount of precipitate produced. It was originally thought that perhaps some sort of inhibition would be obtained. However, as will be seen in the following data the opposite was true in most instances, and the reagin serum actually produced an increase in the amount of precipitate.

#### METHODS AND MATERIALS

Although experimental conditions were purposely varied to some extent, all experiments were carried out in the following general manner.

The reagin serums or the control serums were added to a series of varying dilutions of ovalbumin, and after allowing the mixtures to stand for several hours, rabbit antiovalbumin serum was added. The precipitates were then centrifuged, washed with saline, and analyzed for protein by the Folin-Ciocalteu method.<sup>10</sup>

*Reagin.*—The reagin serums were collected from several individuals, all but one of whom showed some evidence of hypersensitivity to egg white. (Table I.)

Consideration was given to the desirability of heating the serum to 56° C. in order to minimize any variation due to involvement of complement in precipitation,<sup>3</sup> but the possible effect of complement was much less than variations which were obtained with heated reagin serums in a few preliminary experiments.

*Antigen.*—The antigen was an ordinary preparation of ovalbumin which had been recrystallized three times and then lyophilized. The dilutions used in most experiments varied by a factor of 1.5 and were selected to include the zone of maximum precipitation and portions of antigen and antibody excess zones.

*Antiovalbumin.*—The antiovalbumin was taken from a large sample of rabbit serum which had been pooled and lyophilized. A stock solution of antiserum was made by dissolving 8.0 grams of dried material in 100 milliliters of distilled water. Such a solution contained approximately 2.0 milligrams of antibody protein per milliliter.

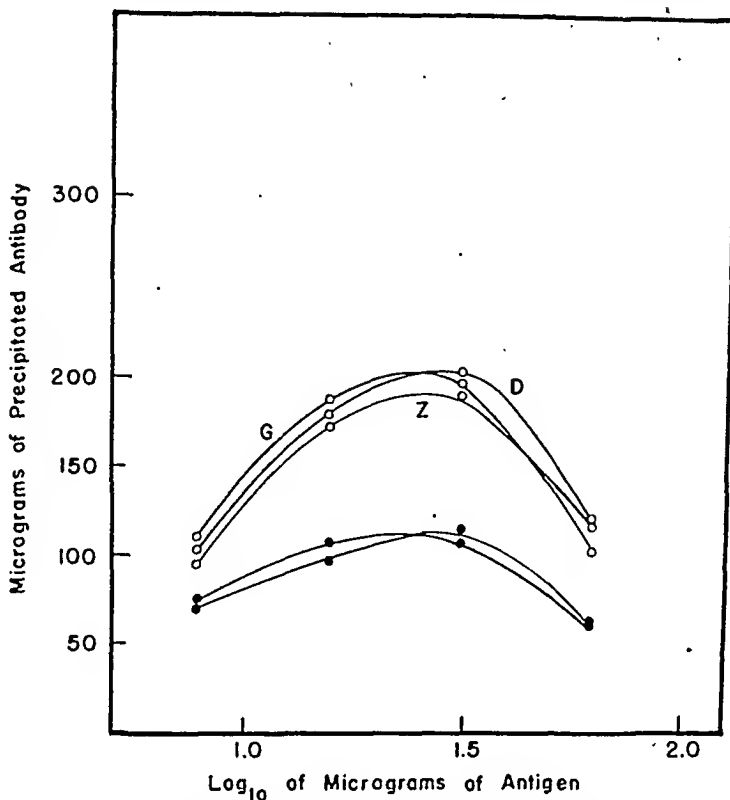


Fig. 1. The effect of antiovalbumin reagin G, Z, and D on the precipitation of ovalbumin and rabbit antiovalbumin. Solid circles are controls of saline and normal serum.

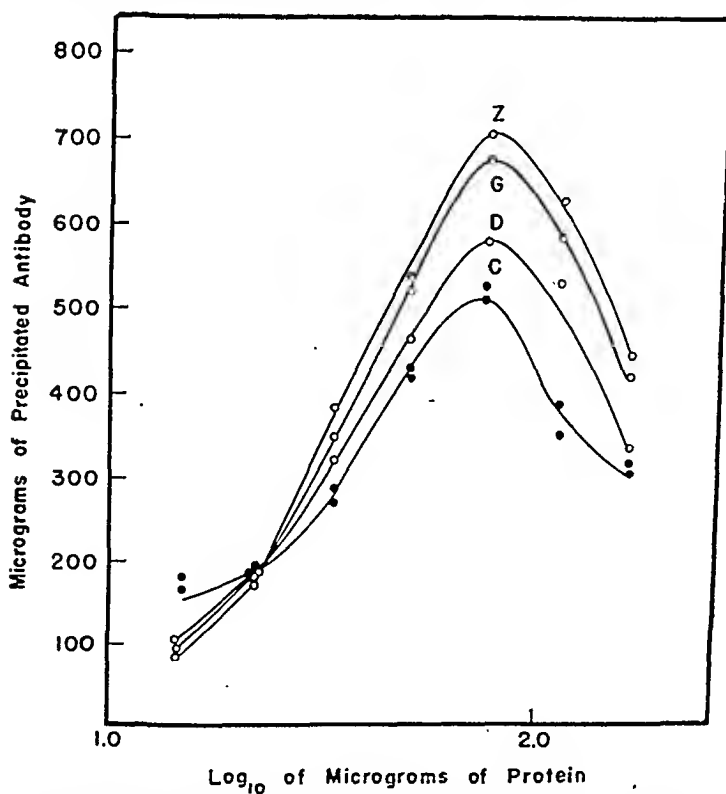


Fig. 2. The effect of antiovalbumin reagin (G, Z, and D) on the precipitation of ovalbumin and rabbit antiovalbumin. Precipitates analyzed at twelve hours.

*Results.*—Although the data of the following preliminary experiments clearly indicate that reagin has a significant effect upon an antigen-antibody precipitation system, the quantitative aspects must await refinements

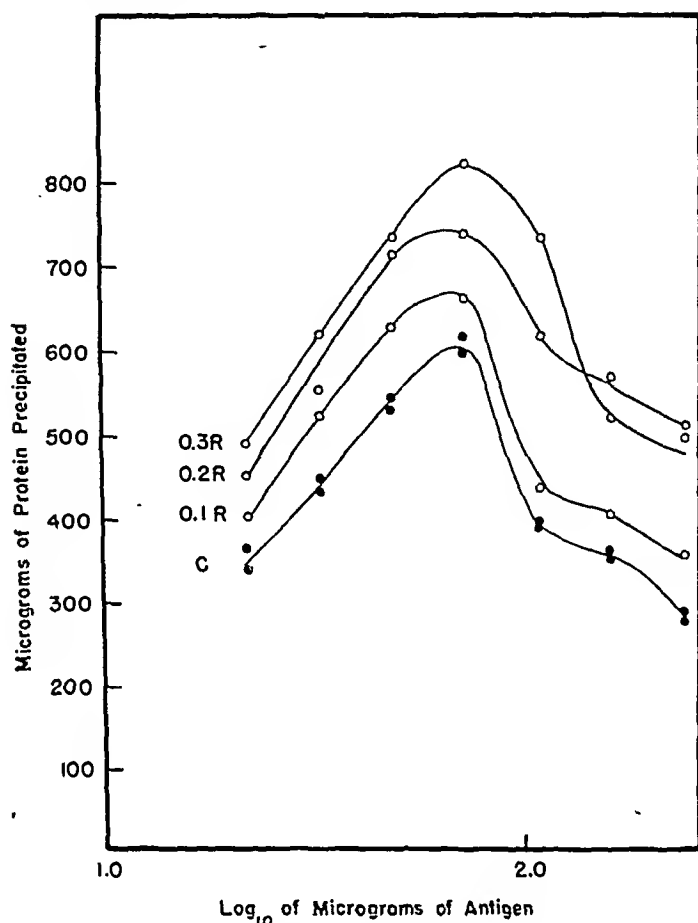


Fig. 3. The effect of various concentrations of antiovalbumin reagin (Z) on the precipitation of ovalbumin and rabbit antiovalbumin. Precipitates analyzed at forty-eight hours.

in methods. For example, the successive steps in antigen dilutions were too great to be certain of the point of maximum precipitation and therefore failed to detect such small shifts in the optimum zone as might have resulted from differences in antibody concentration. Furthermore, the observed experimental deviation of identical tests was as high as  $\pm 30$  micrograms of protein in the region of 500 micrograms total.

#### EXPERIMENTS

*Experiment 1.*—To 0.5 ml. samples of antigen which varied by a factor of 2.0 there was added 0.2 ml. of reagin from three different patients (G, D, and Z) and the mixture allowed to stand for two hours at room temperature. The two controls contained either 0.2 ml. of saline or 0.2 ml. of pooled normal human serum. To each tube 0.5 ml. of a 1:10 dilution of the stock anti-serum solution was then added. The precipitation reaction was allowed to proceed for two hours at room temperature and then about forty hours at 4° C.

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This was the preliminary experiment which showed that instead of producing an inhibition of precipitation as was expected, reagin actually increased the amount of precipitate. The results are shown graphically in Figure 1.

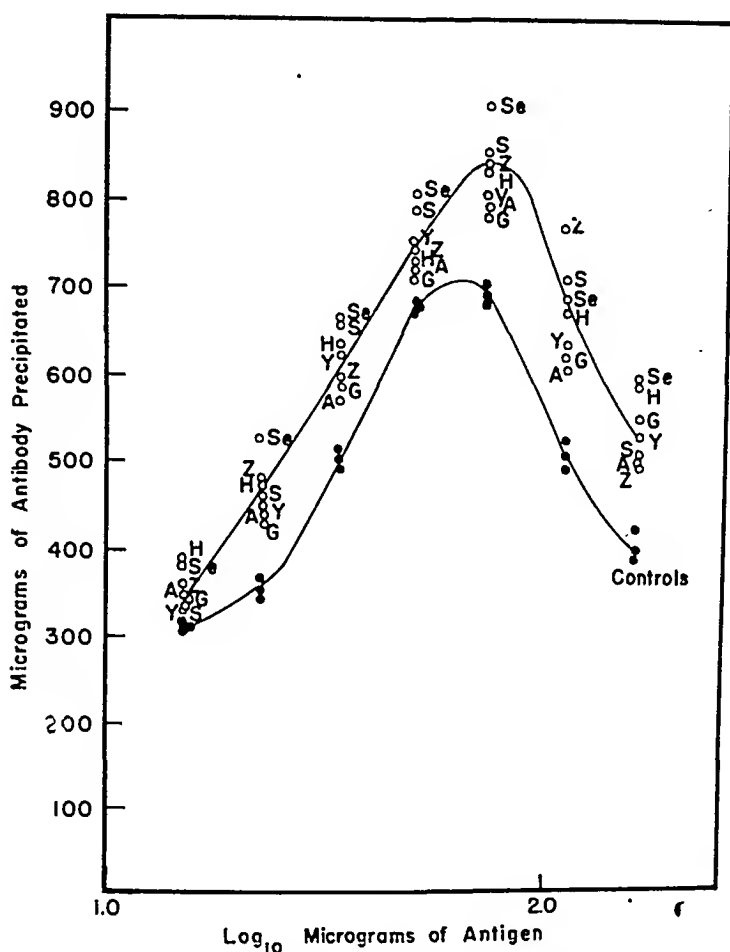


Fig. 4. The effect of antiovalbumin reagin (Se, S, Z, H, Y, A, and G) on the precipitation of ovalbumin and rabbit antiovalbumin. Precipitates analyzed at eighteen hours. Solid circles are controls, one of saline and two of serums from nonallergic persons.

*Experiment 2.*—The same reagins were tested in Experiment 2 but the precipitation system was slightly changed. Antigen dilutions were varied by only a factor of 1.5, the antiserum was diluted 1:2 and the precipitates analyzed twelve hours after the addition of antiserum.

The results, which are given in Figure 2, indicate that in addition to the production of an increase in the precipitate at the equivalence zone, the reagin tended to reduce the amount of precipitate in the antibody excess region. This effect is very similar to that obtained by Pappenheimer<sup>7</sup> and Heidelberger, Treffers, and Mayer,<sup>4</sup> who found that "weak" or univalent antibodies were formed against ovalbumin in horses during the early stages of immunization and that such antibodies decreased the amount of precipitation during the early phase of the precipitation reaction.

*Experiments 3 and 5.*—These two experiments were set up to measure the effect of varying the concentration of reagin serum. In Experiment 3 (Fig. 3) three different amounts of reagin (Z) were tested, namely, 0.1, 0.2, and 0.3 ml. of the undiluted serum. The effect obtained was chiefly that of increasing the amount

of precipitate with, perhaps, a slight tendency for the higher concentration (0.3 ml.) to cause a sharper fall in the curve in antibody excess region.

The fifth experiment was set up in essentially the same manner but with a

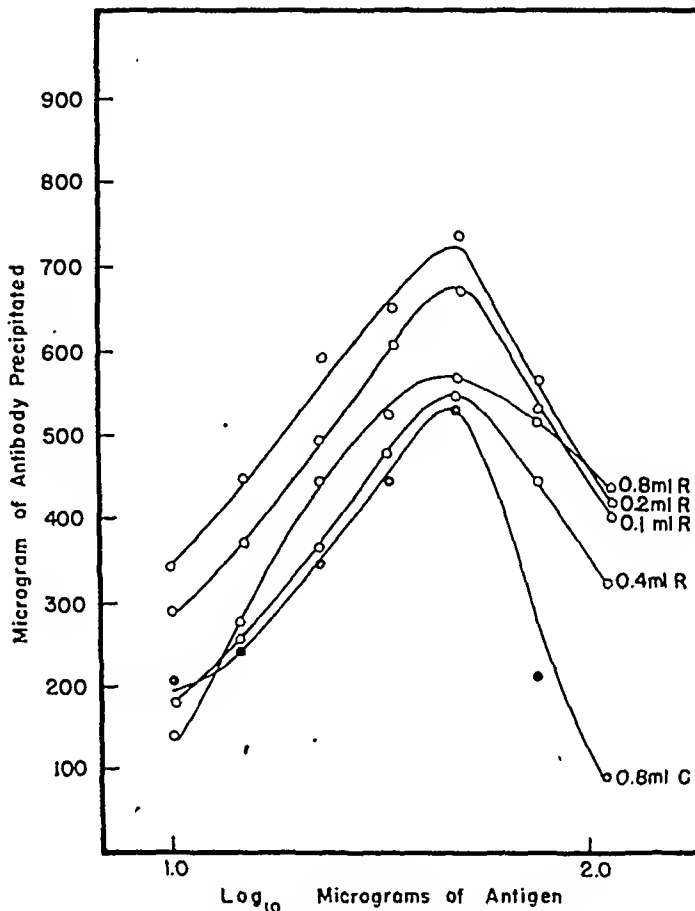


Fig. 5. The effect of varying the concentration of reagent (R) from 0.1 ml. to 0.8 ml. Control (C) was normal serum, and the precipitates were analyzed at forty-eight hours.

greater range of reagent concentrations. In order to have sufficient quantities of reagent serum, it was necessary to pool three samples, Z, G, and A. The results are given in Figure 5 and indicate that large amounts of reagent may actually tend to produce some inhibition of precipitation since the increase due to reagent was much less with 0.4 and 0.8 ml. amounts than with 0.1 and 0.2 ml. amounts.

*Experiment 4.*—The fourth experiment (Fig. 4) showed the effect of serum from seven different egg-sensitive patients. The amounts tested were 0.2 ml. samples in all cases, and the precipitates were analyzed at eighteen hours. Although there was considerable variation in the effect of the various serums, they all tended to increase the amount of precipitate. The curve drawn through the average values may be somewhat misleading since in certain instances there are distinct differences in the shape of the curves. However, it shows the average over-all effect and leaves no doubt that antiovalbumin reagent is incorporated in a precipitative system of ovalbumin and rabbit antiovalbumin. The actual values obtained for the ten different systems are given in Table II.

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TABLE II. THE EFFECT OF ANTIOVALBUMIN REAGIN ON THE AMOUNT OF PROTEIN PRECIPITATED IN AN OVALBUMIN, RABBIT ANTIOVALBUMIN PRECIPITATIVE SYSTEM.

Added to system	Dilutions of antigen and corresponding amounts of antibody precipitated						
	14.97	22.45	32.95	49.38	74.07	110.10	166.06
Nothing	315	340	504	680	690	500	390
0.9% NaCl 0.2 ml.	304	333	505	670	708	488	423
Norm. Serum 0.2 ml.	336	362	488	685	684	539	389
H	389	480	622	717	830	670	589
S	308	471	663	792	848	717	505
Z	357	480	581	745	840	770	495
G	340	437	564	708	763	614	555
A	350	441	630	715	780	606	506
Se	385	530	663	800	912	696	593
Y	326	441	589	748	785	638	531

TABLE III. THE EFFECT OF ANTI-POLLEN REAGIN ON AN OVALBUMIN, RABBIT ANTIOVALBUMIN PRECIPITATIVE SYSTEM.

Material added	Antigen dilution and micrograms of protein precipitated					
	14.97	22.45	32.95	49.38	74.07	110.10
Normal serum 0.2 ml.	514	780	622	488	333	226
Reagin 0.2 ml.	547	717	598	480	329	239

*Experiment 6.*—The sixth experiment is a control with serum from a patient allergic to pollens only (Table III), showing that there was no increase in the amount of protein precipitated.

## CONCLUSIONS

The foregoing experiments clearly show that serum from egg-sensitive individuals contains a type of antibody which attaches to egg albumin and is in some way incorporated in a specific precipitate formed by ovalbumin and precipitating antibody from rabbit antiserum. The data would indicate that the amount of combining reagin is considerable since, in some instances, 0.1 ml. of reagin serum increased the precipitated protein by 200 micrograms. The nature of the reagin antibody or antibodies must await further study but it would appear at present as though the peculiar serological activity of reagin was the result of a lack of a sufficient number of combining groups or groups too weak to afford the formation of insoluble complexes with its antigen, but that such antibodies will attach to a precipitating complex of strong antibody and antigen. It may be speculated that reagin represents the result of a distorted or incomplete antibody-forming mechanism, that is, that reagin is probably a unipolar antibody.

(References on Page 246)

## SOME HELPFUL HINTS FOR MAINTAINING THE EFFICIENCY OF AEROSOL NEBULIZERS

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WITH the increased usage of aerosol nebulizers for vaporizing solutions of epinephrine, penicillin, et cetera, one often meets the problem of obstructions to the capillary tubes of the nebulizer caused by small particles of matter which may form in the solution being nebulized. These obstructions render the nebulizer useless, and the usual method of using

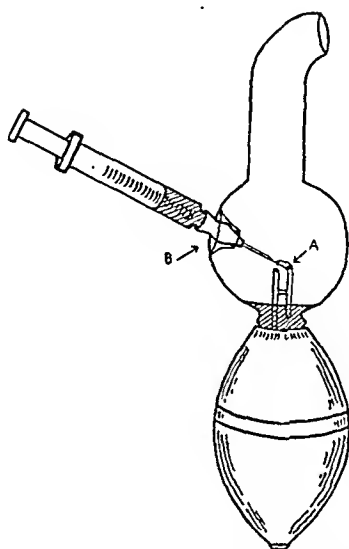


Fig. 1. The needle is inserted through the vent (B), which is usually kept closed by a plug, to force the indicated obstruction (A) out of the capillary tube into the main chamber of the nebulizer.

various types of cleaning solutions is most often not successful since these solutions will not get into the obstructed capillary tubes. Since the tubing is very delicate, it cannot stand much probing, and thus many of these obstructed nebulizers are thrown away as useless.

It is of great importance to inspect the nebulizers regularly to make sure that the capillary tubes are patent. Because of the fine nature of the spray, one can falsely be led to believe that nebulization is occurring, when actually all that is being produced is merely a hissing sound of air over an obstructed tube. This is particularly true in patients who are using the nebulizers at home. We have had several "failures" in asthmatics using 1:100 epinephrine spray, who were relieved when their nebulizers were cleared of obstructions.

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## AEROSOL NEBULIZERS—SELTZER

In the first place, it is best to select a nebulizer which has a vent in the side. This vent is used to put the solution into the nebulizer, but it is also used to get at the tubing for cleaning purposes. The DeVilbiss No. 40 is a good example of this type. There are several types of nebulizers on the market which have no vent on the side, and the solutions are poured into the top of the vaporizer. These types, if obstructed, are very difficult to clean. Here, then, is a hint to manufacturers: all nebulizers should be arranged so that the tube which is not connected with the bulb will face the vent in the side of the nebulizer (Fig. 1). With this arrangement it is simple to keep the nebulizer free from obstructions.

The obstructions which occur always take place in the capillary tube which has no direct connection with the blast of air, and all the blowing of solvents through the nebulizer will not remove the obstruction, but will rather tend to wedge it more firmly into place. However, if a fine long needle is put on a small syringe filled with water, and directed through the vent in the side of the nebulizer, so that the point of the needle rests on the opening of the obstructed tube (Fig. 1), then a small squirt of water from the syringe will flush the obstruction out of the capillary tube into the main chamber of the nebulizer, where it can be readily washed out. This can be done in a few seconds without damage to the delicate tubes, and it restores the nebulizer to full efficiency.

Thus, one can see the value of using a nebulizer which allows access to the capillary tubes. The use of other types of nebulizers will result in shorter periods of use.

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### Penicillin Sensitivity

In view of the increasing reports of penicillin sensitivity, the following abstract, which appeared in *The Chemist and Druggist*, September 8, 1945, was furnished upon request, through the courtesy of the editor. The note on Sycosis Barbae was abstracted from the *British Journal of Dermatology and Syphilis*.

**SYCOSIS BARBAE**—The "British Journal of Dermatology and Syphilis" (May-June, 1945) records the successful use of a penicillin cream in cases of sycosis barbae. The formula for the cream base was:—

Distilled water .....	250 c. c.
Lanette Wax SX .....	50 gm.
Castor oil .....	50 c. c.

To this, an amount of 200 units of penicillin per gm. was added. In nineteen cases where the predominant organism was found to be a penicillin-sensitive strain of staphylococcus, the cream was used with benefit. In thirteen with a history of more than a year, six were cleared within an average of six weeks, and six others showed improvement within this period. Of the six patients with a history of less than a year, four were cleared in an average of two and a half weeks and one was improving over a period of five weeks.

# Department of Clinical Pathology and Laboratory Procedures

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## THE WELTMAN REACTION AS A DIAGNOSTIC AID

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WITH the advance of effective antibiotics useful in the treatment of respiratory infections that have in the past resisted other forms of therapy, it has become more important in the management of asthma to be able to differentiate between true allergic asthma and infectious bronchial asthma, or to be able to detect a low-grade infectious process which has been grafted on an original allergic asthma. Regardless of one's opinion as to the mechanics by which chronic infection of the respiratory passages complicates the asthmatic picture, it is desirable to detect such infection so as to institute treatment to overcome it. Such a differential diagnosis is by no means always easy, and any additional diagnostic procedure of value should be welcome.

In 1941 Dees<sup>1</sup> called attention to the value of the Weltman coagulation reaction in the diagnosis of the presence and degree of infection in allergic individuals. Although the conclusions reached in her paper were strikingly in support of its value, the test has gained little popularity. In view of the simplicity of the technique involved, it is surprising that this is so. This short communication is to call attention again to this valuable procedure. The technique of the test is simple, and the essential reagent is easily prepared and stable.

Quoting Dees' paper: "The technique of the test as described by Weltman is as follows: Ten dilutions of  $\text{CaCl}_2 \cdot 6\text{H}_2\text{O}$  solutions ranging from 0.1 to 0.01 per cent are prepared from a stock solution of 10 per cent  $\text{CaCl}_2 \cdot 6\text{H}_2\text{O}$ . Five cubic centimeters of each of these solutions are measured into small test tubes which are numbered from one to ten to correspond with the dilutions. To each tube is added exactly 0.1 cubic centimeter of unhemolyzed serum. The contents of the tubes are thoroughly mixed and placed in their rack in a boiling water bath for fifteen minutes. They are then removed and the number of tubes in which coagulation is present is noted. Normal serum regularly coagulates in the first six tubes of the series in concentrations from 0.1 per cent through 0.05 per cent  $\text{CaCl}_2 \cdot 6\text{H}_2\text{O}$ . In most instances there is turbidity in addition to flocculation in more than the first six tubes. This turbidity is not considered, however, in determining the end point of the test, since degrees of turbidity are difficult to estimate, are variable, and show no apparent relationship to findings in normal and pathologic states. The

## CLINICAL PATHOLOGY AND LABORATORY PROCEDURES

values are expressed as a coagulation band corresponding to the number of tubes showing flocculation. For example, normal serum is said to have a coagulation band of six, or  $CB=6$ ."

In the interpretation of the test, any reading below a coagulation band of six is indicative of some type of acute or chronic inflammatory process. The test is not subject to a great many variable factors, as are the white count and the sedimentation rate, and is to be interpreted identically in both children and adults.

In our laboratory, this test has become the most dependable single indicator of an inflammatory disease which we have at our disposal. The original article should be consulted, as it is an excellent presentation and is supplemented by a complete biography up to the date of its writing. This test is one that requires no elaborate apparatus nor complicated technique. It is quite applicable for use in a small laboratory and certainly deserves a wider use.

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### Acute Poison Ivy Dermatitis

(Continued from Page 223)

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(Continued from Page 242)

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# Editorial

*The opinions expressed by the writers of editorials in the ANNALS are individual and do not necessarily represent the group opinion of the Board or of the College.*

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## A REMARKABLE MEETING OF THE NEW YORK ACADEMY OF SCIENCES

Though the New York Academy of Sciences likes to serve cocktails among the dinosaurs,\* it is itself the least fossil organization imaginable. Its conferences on selected topics in biology are becoming an important feature in interscience relations. The attention of the readers of this journal previously was directed to a conference on allergy which was held on April 25 and 26. The most important aspects of the problem were presented in a series of papers of high academic level. They will be published in *extenso* in the *Annals of the New York Academy*. Two of the topics were of such immediate interest to the practicing allergist that they merit a few words of comment at this time.

Samuel Karelitz, Mt. Sinai Hospital of New York, presented the results of his work on serum sickness. Some of this work has been published in the *Journal of Immunology*, but its full impact came only to the fore at this meeting. As was already known from v. Pirquet and Schick, serum disease is not correlated with precipitating antibody (which may or may not be present in the serum of patients). In serum taken from patients three to twelve days after injection with equine antitoxin, Karelitz demonstrated a not-precipitating antibody demonstrable by passive transfer of generalized reaction, by local sensitization both to locally (intradermally) applied and to intravenously injected antigen, and by inverse passive sensitization. It is heat stabile (90 minutes 56°C. or 60 minutes 60°C.), and has a neutralizing effect, insofar that a properly balanced mixture of Karelitz' antibody and antigen (= equine protein) is nonreactive if introduced into the sensitized skin. It may be present for a considerable length of time; in one patient it could be demonstrated three years after serum treatment. The properties of the antibody of serum disease resemble those of the heat stabile, neutralizing antibody of poli-nosis. In function, however, there is the thought-provoking difference, that the antibody of Karelitz induces sensitization, whereas the antibody of Cooke and Loveless is protective.

One session of this meeting was dedicated entirely to familial non-reaginic allergy. Milo G. Meyer from Michigan City, Indiana, reported on about 100 patients and Alan Johnston of Indianapolis on a smaller number of patients with assorted allergies. Edward T. Whitney of Boston reported on twenty patients with pruritus ani. (One important detail:

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\*In the famous Dinosaur Hall of the American Museum of Natural History.

he found that only those cases of pruritus which did not show signs of local changes represented familial nonreaginic allergy.) Thus, Coca's clinical syndrome of idioblapsis and the therapeutic effect of elimination of the causative allergens were confirmed from three independent sources. These clinical papers were complemented by a review of Locke on the correlation of familial nonreaginic allergy and susceptibility to common colds, and by a report by A. F. Coca on the results of sympathectomy in three desperate cases of idioblapsis (see May issue of the *ANNALS*).

A. J. W.

#### ASTHMA AS A CAUSE OF DEATH IN CHILDREN: REPORT OF A CASE.

Pedrero, José. (Muerte por asma en niño: reporte de un caso). *Bol. Soc. cubana de pediat.*, 17:95-99, March 1945.

The author reports the case of a white boy, thirteen years old, who entered the hospital on August 8, 1942, at 5 a.m. because of an acute attack of asthma which had occurred suddenly a few hours before. The usual measures did not stop the increasing dyspnea; cyanosis appeared, and death occurred at 8:30 a.m. There was no autopsy.

*Family History.*—Father suffered from gastrointestinal allergy, especially to fish, marked by urticaria. A younger brother had died of anaphylactic shock after an injection of anti-tetanus serum.

*Personal History.*—Born at term, the child was breast-fed and had a normal development. In January, 1936, his adenoids were removed, and two months later he had his first attack of asthma, which was moderately severe with vomiting, and lasted some hours. From this time on, the attacks occurred every two or three weeks and increased in severity. In April, 1937, he had measles and, shortly after, urticaria lasting for several months.

In March, 1941, he came to the allergy department. He was then twelve years old and weighed 63 pounds. Intradermal tests were positive for oranges, spinach, white beans, chocolate; positive reactions to house dust, cat's hair, and wool. He was moderately positive to *Staphylococcus albus*, *Streptococcus hemolyticus* and *Micrococcus catarrhalis*. Instruction was given to avoid the allergic substances and a month later he had gained two pounds and had been free from attacks. After that he was not seen again, but his history indicated that the attacks had recurred and that he had had an attack of mumps a month and a half before his death.

Death caused directly by asthma used to be considered extremely rare and is probably rather unusual in proportion to the great frequency of asthma and other allergic diseases. Up to 1926 only eleven cases had been published, the majority of which were in adults. However, in 1928, Bivings reported a case in a child of ten months, and Waldbott cited one in a sixteen-months-old child. Thieme and Sheldon studied seven cases, of which two were children.

There are many theories as to the mechanism of death in asthma, none of which alone is sufficient to explain the individual cases. Among them are: inhibition of cardiac function, sudden myocardial insufficiency, toxemia, dehydration, et cetera. The author believes that dehydration and disturbances of acid base equilibrium may play a large part.

## FALL GRADUATE INSTRUCTIONAL COURSE

The American College of Allergists announces its Fall Graduate Instructional Course in Allergy to be held under the auspices of the College of Medicine, University of Cincinnati, Cincinnati, Ohio, November 3-8 inclusive. Hotel headquarters will be at the Netherland Plaza.

The faculty consists of more than forty outstanding physicians and scientists from prominent medical centers and colleges in the United States and Canada.

Each course presents a complete, up-to-the-minute study of the entire field of allergy. The program covers fundamentals such as physiology, immunology, psychosomatics, and pathology; special allergies such as mold, food, bacterial, and physical; pharmacology of drugs used in the treatment of allergy; preparation of allergenic extracts; techniques of skin testing; and the determination of allergic history. Adequate consideration is given to specific diseases such as bronchial asthma, allergic bronchitis, bronchiectasis, Loeffler's syndrome, Ménière's disease, hay fever, and aural, ocular, vascular, joint and neuro allergy. There are also comprehensive symposiums on dermatologic and pediatric allergy.

The fee for the course is \$100.00. The course has been approved by the Veterans Administration for the training of veterans under Public Law 346. There will be special bus service between the hotel and the Medical College.

Early registration is urged because the number of students may have to be limited due to the facilities of the hotels and the Medical College.

Make all reservations for the course and hotel accommodations directly with the secretary, Dr. Fred W. Wittich, 423 LaSalle Medical Building, Minneapolis, Minnesota. In making your reservation please state the exact time of your arrival and departure and whether you want a single room or wish to share one with another registrant. The number of single rooms is limited.

### FACULTY

Harold A. Abramson, M.D., F.A.C.A., Assistant Professor of Physiology, Columbia University; Associate Physician in Allergy, Mount Sinai Hospital, New York, New York.

William B. Bean, M.D., Associate Professor of Medicine, Medical College, University of Cincinnati, Cincinnati, Ohio.

Harry S. Bernton, M.D., Professor of Hygiene, Medical and Dental Departments, Georgetown University; Clinical Specialist in Allergy, Allergen Research Division, Bureau of Agriculture and Industrial Chemistry, United States Department of Agriculture, Washington, D. C.

Irvin H. Blank, Ph.D., Research Associate in Dermatology, Harvard University Medical School, Boston, Massachusetts.

Milton G. Bohrod, M.D., Director of Laboratories, The Rochester General Hospital, Rochester, New York.

Ethan Allan Brown, M.D., F.A.C.A., M.R.C.S., London, L.R.C.P., England; Tufts College Medical School, Boston, Massachusetts.

Hal M. Davison, M.D., F.A.C.A., Chief of Medical Division, Lecturer in Allergy and Internal Medicine, Georgia Baptist Hospital, Atlanta, Georgia.

Vincent J. Derbes, M.D., F.A.C.A., Instructor of Medicine, Tulane School of Medicine, New Orleans, Louisiana.

Stanley Dorst, M.D., Dean of Medical College, University of Cincinnati, Cincinnati, Ohio.

E. E. Ecker, M.D., Professor of Pathology, Western Reserve University, Cleveland, Ohio.

Stephan Epstein, M.D., F.A.C.A., Marshfield Clinic, Marshfield, Wisconsin.

Jonathan Forman, M.D., F.A.C.A., Professor of History of Medicine and Lecturer on Allergy, Ohio State University, Columbus, Ohio.

## FALL GRADUATE INSTRUCTIONAL COURSE

- Leon Goldman, M.D., Associate Professor of Dermatology Medical College, University of Cincinnati, Cincinnati, Ohio.
- French K. Hansel, M.D., F.A.C.A., Associate Professor of Otolaryngology, Washington University, School of Medicine, St. Louis, Missouri.
- Bayard T. Horton, M.D., F.A.C.A. (Hon.), Associate Professor of Medicine, Mayo Foundation, Rochester, Minnesota.
- R. F. Hughes, M.D., F.A.C.A., Royal Victoria Hospital, Hamilton, Ontario, Canada.
- D. E. Jackson, M.D., Professor of Pharmacology, Medical College, University of Cincinnati, Cincinnati, Ohio.
- C. R. K. Johnston, M.D., F.A.C.A., Section on Allergy, Cleveland Clinic, Cleveland, Ohio.
- Morris A. Kaplan, M.D., F.A.C.A., Medical College, University of Illinois, Chicago, Illinois.
- Foster Kennedy, M.D., Professor of Neurology, Cornell University Medical College, New York, New York.
- J. Harold Kotte, M.D., Assistant Professor of Medicine, Medical College, University of Cincinnati, Cincinnati, Ohio.
- Hugh A. Kuhn, M.D., F.A.C.A., Hammond, Indiana.
- Mary H. Loveless, M.D., F.A.C.A., Assistant Professor of Medicine, Cornell University Medical College, New York, New York.
- John H. Mitchell, M.D., F.A.C.A. Assistant Professor, Department of Medicine, Director of Out-Patient Clinic, Ohio State University, Columbus, Ohio.
- William F. Mitchell, M.D., F.A.C.A., Columbus, Ohio.
- Paul Moore, M.D., Muncie, Indiana.
- M. Murray Peshkin, M.D., F.A.C.A., Instructor, College of Physicians and Surgeons, Post Graduate Medical Extension, Columbia University, New York, New York.
- George Piness, M.D., Associate Clinical Professor of Medicine, University of Southern California; Chief of the Allergy Clinic, Children's Hospital, Los Angeles, California.
- Homer E. Prince, M.D., F.A.C.A., Associate Professor of Medicine, Baylor University, School of Medicine, Houston, Texas.
- Bret Ratner, M.D., F.A.C.A., Clinical Professor of Pediatrics, New York University College of Medicine; Director of Pediatrics, Sea View Hospital, New York, New York.
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- George E. Rockwell, M.D., F.A.C.A., Editorial Board, Annals of Allergy, Milford, Ohio.
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- A. B. Schwartz, M.D., Milwaukee, Wisconsin.
- Howard L. Stitt, M.D., F.A.C.A. (Assoc.) Clinical Instructor, Children's Hospital; Medical College, University of Cincinnati, Cincinnati, Ohio.
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- Leon Unger, M.D., F.A.C.A., Associate Professor, Department of Medicine, Northwestern University Medical School, Chicago, Illinois.
- George L. Waldbott, M.D., F.A.C.A., Head of Allergy Department, Harper Hospital, Detroit, Michigan.
- Charlotte Wiedemer, M.D., F.A.C.A., Instructor of Medicine, Medical College, University of Cincinnati, Cincinnati, Ohio.
- Orval R. Withers, M.D., F.A.C.A., Associate Professor of Medicine, School of Medicine, University of Kansas, Kansas City, Kansas.
- Fred W. Wittich, M.D., F.A.C.A., Managing Editor, Annals of Allergy, Minneapolis, Minnesota.
- Roger P. Wodehouse, Ph.D., F.A.C.A. (Assoc.) Associate Director of Research in Allergy, Lederle Laboratories, Pearl River, New York

## FALL GRADUATE INSTRUCTIONAL COURSE

### PROGRAM

*Monday, November 3, 1947*

#### FUNDAMENTALS OF ALLERGY

- 8:30- 9:30 Registration.  
9:30- 9:45 Address of Welcome, Dean Stanley Dorst.  
9:45-10:30 "The Physiology of Allergy," Dr. Fred W. Wittich.  
10:30-11:15 "Immunological Aspects of Allergy," Dr. Mary Loveless.  
11:15-12:15 "The Clinical Significance of Recent Chemical Studies of Allergens," Dr. Harry S. Bernton.  
12:15- 1:15 "Basic Principles of Allergy"—Moving Pictures, Dr. Bret Ratner.  
2:15- 3:15 "Psychosomatic Factors in Allergy," Dr. John H. Mitchell.  
3:15- 3:45 "Present Status of Antihistamine Drugs," Dr. Jonathan Forman.  
3:45- 5:00 "Pharmacology of the More Important Drugs Used in Allergy," Dr. D. E. Jackson.  
7:00 Informal Dinner—Speaker: Dr. Hal M. Davison.

*Tuesday, November 4, 1947*

#### FUNDAMENTALS OF ALLERGY

- 9:00- 9:30 "X-Ray in Allergy; Diagnosis and Treatment," Dr. Paul Moore.  
9:30-10:30 "Bacterial Allergy," Dr. E. E. Ecker.  
10:30-11:15 "Food Allergy," Dr. Hal M. Davison.  
11:15-11:45 "Balanced Diet," Dr. William B. Bean.  
11:45-12:30 "Elimination Diet," Dr. Herbert J. Rinkel.  
12:30- 1:15 "Physical Allergy," Dr. Harold A. Abramson.  
2:15- 3:15 "The Preparation and Standardization of Extracts," Dr. Morris A. Kaplan.  
3:15- 4:00 "Skin Testing: Technique and Interpretation," Dr. William F. Mitchell.  
4:00- 4:30 "History Taking," Dr. J. Warrick Thomas.  
4:30- 5:00 Demonstration, Dr. Charlotte Wiedemer.

*Wednesday, November 5, 1947*

#### RESPIRATORY ALLERGY

- 9:00- 9:45 "Pathology of Asthma," Dr. Milton G. Bohrod.  
9:45-11:15 "Bronchial Asthma: Diagnosis, Management and Treatment," Dr. Leon Unger.  
11:15-12:00 "Aerosol Treatment of Asthma," Dr. Harold A. Abramson.  
12:00-12:30 "Bronchoscopy in the Treatment of Asthma," Dr. Howard L. Stitt.  
12:30- 1:15 "Cardiac Asthma and Cor Pulmonale," Dr. J. Harold Kotte.  
2:15- 3:15 "Allergic Bronchitis, Bronchiectasis and Loeffler's Syndrome," Dr. Vincent J. Derbes.  
3:15- 3:45 "Allergic Rhinitis," Dr. French K. Hansel.  
3:45- 4:15 "Aural Allergy," Dr. Hugh A. Kuhn.  
4:15- 5:00—"Ocular Allergy," Dr. A. D. Ruedemann.  
8:00-10:00 Clinic.



## FALL GRADUATE INSTRUCTIONAL COURSE

*Thursday, November 6, 1947*

### HAY FEVER

- 9:00- 9:30 "Botany of Hay Fever Plants," Dr. Roger P. Wodehouse.  
9:30-11:00 "Hay Fever: Diagnosis, Treatment and Management," Dr. George E. Rockwell.  
11:00-11:45 "Pollen Respiratory Allergy with Negative Cutaneous Reactions," Dr. M. Murray Peshkin.  
11:45-12:45 "Mold Allergy: Symptoms, Diagnosis and Treatment," Dr. Homer E. Prince.  
12:45- 1:15 "Pollen Counts and Demonstration," Dr. Charlotte Wiedemer.  
2:15- 3:15 "Vascular Allergy," Dr. Milton G. Bohrod.  
3:15- 5:00 "Clinical Use of Histamine," Dr. Bayard T. Horton.

*Friday, November 7, 1947*

### DERMATOLOGIC ALLERGY

- 9:00- 9:45 "Atopic Dermatitis," Dr. Stephan Epstein.  
9:45-10:45 "Contact Dermatitis," Dr. Leon Goldman.  
10:45-11:25 "Urticaria," Dr. R. F. Hughes.  
11:25-12:20 "Soap and Other Detergents," Dr. Irvin H. Blank.  
12:30- 1:30 "Drug Allergies," Dr. Ethan Allan Brown.  
2:30- 3:00 "Joint Allergy," Dr. Bela Schick.  
3:00- 4:15 "Neuro Allergy including Migraine," Dr. Foster Kennedy.  
4:15- 5:00 "Unusual and Obscure Conditions of Allergies," Dr. C. R. K. Johnston.

*Saturday, November 8, 1947*

### PEDIATRIC ALLERGY

- 9:00- 9:45 "Management of the Pre-Allergic Child," Dr. Bret Ratner.  
9:45-10:30 "Characteristics of the Allergic Child," Dr. A. B. Schwartz.  
10:30-11:45 "Special Problems in Treatment and Management of Asthma in Children," Dr. George Piness.  
11:45-12:45 "Infantile Eczema," Dr. Albert V. Stoesser.  
12:45- 1:30 "Gastro-intestinal Allergy in Children," Dr. Orval R. Withers.

On Tuesday, Thursday and Friday evenings from 8:00-10:00 p.m., there will be instructors in Parlors A and B, Netherland Plaza Hotel, so that if they desire, students may visit, ask questions and have informal discussions.

Speaker at Large and Director of Round Table Discussion, Dr. George L. Waldbott.

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# Progress in Allergy

## HAY FEVER

### A Review of the Literature of 1946

MORRIS A. KAPLAN, M.S., M.D., F.A.C.A.

and

NORMAN J. EHRLICH, M.S., M.D.,

Chicago, Illinois

Spain<sup>105</sup> summarized our problem in hay fever by stating, "While the concept of the hay-fever reaction may be simple, its explanation is not. Many questions remain to be satisfactorily answered. Such questions pertain to the allergic behavior of the victim, to the chemical structure of the pollen antigen with the assay of its activity, and to the nature of the allergic reaction which implements the hay fever condition, and upon which are based methods of specific diagnosis and treatment, both largely empirical. There is yet no satisfactory explanation as to why only 2.3 per cent of the population of the United States develop hay fever, despite the fact that all are equally exposed to pollen contacts." He continued by stating that, "To the worker in allergic problems, the preparation and standardization of pollen extracts is of prime importance; the lack of uniformity and agreement in these matters is disturbing."

## BOTANY

Small and Small,<sup>101</sup> from a very comprehensive, extensive, and adequate survey of various regions in Southern California, concluded that Southern California had perhaps the greatest number and widest variety of hay fever-producing plants in the United States; however, the quantity of pollen contaminating the air of the cities was not very large. The ragweed and grass seasons, however, were much longer than elsewhere. Harsh,<sup>53</sup> in his report on pollinosis in Imperial County, California, and Yuma, Arizona, discussed the abundance of pollens, pollinating dates, relative pollinating ability, size of pollen grains, and pollen toxicity. Harsh suggested that the skin reaction of the patient should be considered first in relation to the abundance of the reacting species and then in relation to the amount of pollen produced and its bouyancy as indicated by the size of the grains. In *Queries and Minor Notes*,<sup>86</sup> a question was asked about the pollen content in Los Angeles. Durham notes that, during July, August, September, and October, the Western ragweed there was equal to about 2.5 per cent of that in Chicago. During March and November, there were small amounts of *Alternaria* and *Hormodendrum* molds, and grass and chenopod-amaranth pollens were less than ragweed, and a very small amount of sage. Bermuda grass was widely used in California for lawns. Targow<sup>109</sup> stated that the following ragweed species also were found in California: *Ambrosia psilostachya* and *Franseria acanthicarpa*. However, their pollen count was very low.

Bieberdorf and Hampton<sup>13</sup> discussed airborne fungi in the San Antonio, Texas, area, as ascertained from exposure plates and vaseline-coated slides. Mold spores were found on the plates and slides almost each day, and high counts were recorded during the entire survey. Nine genera made up 90 per cent of the molds encountered. *Hormodendrum* and *Alternaria* were highest in incidence by the plate method, whereas, in the slide studies, *Alternaria* and *Helminthosporium* were found most frequently. No definite seasonal trends of the individual molds was noted. Of 1,515

Dr. Ehrlich is an Associate Member of the American College of Allergists.

## PROGRESS IN ALLERGY

patients with proved allergic disease, 12.28 per cent showed definitely marked skin reaction to one or more molds, as compared to 0.012 per cent of 488 normal controls.

Larsen and Weller<sup>55</sup> reported that ragweed was appearing in Hawaii. Of 100 patients with positive skin tests, 30 per cent reacted to dust, 28 per cent to Bermuda grass, 20 per cent to algaroba, 30 per cent to amaranth, 12 per cent to Johnson grass, and 10 per cent to sugar cane. It was noted that the pollen count in this area varied with humidity, wind, temperature, and light. Also, there was an interrelation between these factors that caused sudden increase in the pollen count at varying times from 2 a.m. to 6 p.m.

Hyde and Williams<sup>57</sup> conducted a grass pollen survey near Cardiff, Wales, from June 15 to June 22, 1944. Four sets of slides were exposed. Two were impact slides attached in a vertical position to a weather vane and the other two were gravity slides in an apparatus similar to that described by Durlham. The sites chosen for exposure were a patch of grassy vegetation and the top of a building. The slides were exposed for two-hour periods throughout the day and observations were made on sunshine, rain, wind direction, and wind velocity. These data were plotted on a graph and it was noted that all four graphs moved up and down in unison, with no apparent time lag between the ground and roof catch. A morning and afternoon rise was noted at both sites every day; however, the impact catch always was ten times greater than the gravity catch at each site. Highest counts were encountered following several hours of bright sunshine. Afternoon counts were relatively low on cloudy days. Variation in pollen counts were more marked on the ground than on the roof site and were closely related to the flowering of the principal grasses in the area. Low counts during hours of darkness were correlated with the total cessation of flowering during that period. It was concluded that there is a diurnal variation in grass pollen counts that can be correlated with the incidence of bright sunshine and with the flowering of neighboring grasses. The impact catch appeared to be a more sensitive index of grass pollen liberation than did the gravity method.

Hyde and Williams<sup>57</sup> also made studies at Cardiff on the incidence of *Alternaria* spores by counts, using the gravity slide method. They observed that *Alternaria* spores formed a normal and regular part of the annual spore rain at Cardiff and were present in the spring and summer, in greatest numbers during the months of June through September. During the late autumn and winter months, they virtually were absent. The slide collection during June through September totalled 646 spores in 1942 and 726 in 1943. The period of highest incidence coincided with that of the highest mean temperature. The catch during the summer months varied considerably from day to day. There seemed to be no relation between wind velocity and catch. On certain occasions, rainfall resulted in a temporary, although at times marked, diminution in the catch. Some figures were presented, comparing the daily catch in Wales with places in the Eastern United States. The authors expressed the opinion that the spores in Cardiff originated in cereals growing in the vicinity.

Boggs<sup>15</sup> reported on a patient with early spring hay fever, apparently due to the effect of pine pollen. Ordman<sup>62</sup> reported on fourteen patients with winter-spring hay fever and allergic conjunctivitis associated with cypress pollen sensitivity. He discussed the management of these patients in detail, beginning hyposensitization early in April and continuing until the middle of June.

Lima et al.,<sup>67</sup> stated that hay fever was unusual in Brazil, although the incidence of other allergic manifestations apparently was similar to that in other countries. Up to the time of their report, apparently only one case of hay fever had been reported—a Spanish patient. It might be significant that no incidence of typical hay fever had been reported among native Brazilians. Various opinions have been expressed to explain why pollinosis is rare in Brazil: (1) lack of susceptibility of

Brazilians, (2) meager density of pollen grains in the atmosphere, (3) shortness of pollination periods, and (4) weak allergenic capacity of the pollen. The authors, however, reached no conclusion on this interesting subject. According to their observations, among Brazilians the percentage of cutaneous sensitivity to pollen was very low. They reported on the principal anemophilous plants of Brazil.

Giscafre<sup>47</sup> wrote that the ornamental *L. lucidum*, that is cultivated commonly in the streets of the city of Santa Fe, was as serious a cause of hay fever as ragweed and grasses, in spite of its short pollen period.

Alvarez,<sup>3</sup> discussing pollinosis in Havana, noted that the prevailing winds, the geographic situation, the torrential rains in the summer, and the drought in winter did not favor the wide distribution of pollens in the air. In Cuba, the main pollinosis-producing species of plants did not exist. *Ambrosia* was rare. Relatively significant amounts of pollen from only the following plants were found in aerobiological studies: *Cynodon dactylon* (Bermuda grass), *Parthenium hysterophorus* (feverfew), *Mangifera indica*, and *Phoenix dactylifera*. *Casuarina* (Australian Pine) pollen presented a certain seasonal type and was the most abundant, but no person with hypersensitivity to it could be found. Hypersensitivity to pollen was rare. In a clinical series of 653 patients with respiratory allergy, only 4.1 per cent were found to be sensitive to pollen. On the whole, Havana possessed an ideal climate for clinical improvement in pollinosis sufferers.

From Australia, Morton<sup>78</sup> presented a comprehensive approach to the problem of the botany of an area and its relation to clinical allergy of the upper respiratory tract. The botanical factors in the investigation of seasonal hay fever were recorded. He gave a short description of his area, as to topography and meteorology. The potential hay fever flora of his district were examined and he noted that the most common cause of seasonal allergy of the hay fever and asthma type was anemophilous pollen of weeds and grasses. Hypersensitivity of patients to pollen of weeds alone was unusual, but generally was associated with hypersensitivity to pollen of grasses. Tree pollens played only a minor rôle in seasonal hay fever. He observed that the onset, severity, and duration of the hay fever season were bound intimately to the prevailing meteorological conditions and varied from year to year.

Woringer<sup>116</sup> observed that allergy to the castor oil plant (*Ricinus*) occurred in handlers and laboratory workers. Clinically, the condition resembled pollinosis. The skin and mucous membranes reacted vigorously to extracts. The allergenic principle was present in the leaves as well as in the seeds. An active specific antibody was demonstrated in the blood, and the allergen was different from toxin ricin that could be isolated chemically. Sensitization occurred from inhalation.

Many attempts have been made to control and eradicate weeds. Both local and national government agencies have instituted laws which made it mandatory for a person owning land on which weeds are growing to eradicate them before they can pollinate. Recently, a bill was introduced in Congress, awarding a fund to set up methods for such a program. Now there is greater hope for the success of such a program, by the use of the so-called chemical weed killers. The state of Michigan intends to institute such a program. Grigsby<sup>48</sup> described such a method. A stock solution of di-nitro-ortho-secondary-butyl phenol, containing 4 pounds of the ammonium salt in one gallon of Diesel oil in kerosene 50 to 100 ml per gallon, completely killed ragweed within six hours and pollen release was stopped. Water solutions of this material killed more slowly and, using the same dilution, killing was incomplete. Other chemicals were tested but were not as effective. These results indicated that it was possible to stop pollen production in ragweed with chemical sprays. In the concentration used, most of the materials in this series were more or less toxic to cultivated crops. Smith,<sup>102,103</sup> discussing similar pollen control, stated that an aqueous compound of 2, 4, di-chlorophenoxyacetic acid of 1,000 ppm prevented pollen

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shed if used early in the flowering stage. Experiments with a fog machine indicated that it was more economical than a spray. In *Queries and Minor Notes*,<sup>85</sup> in a discussion on a de-pollinating program, it was stated that chemical destruction was possible, but that it depended on the particular situation. As an example, if a community was insulated on all sides by a wide strip of water or forested lands, or if weeds were well established, it was almost impossible because of the longevity and abundance of viable seeds in the soil. Annual riddance could be accomplished by uprooting the weeds. This problem could be solved; however, the effort would have to be national and on a continuous basis because pollen, due to its buoyancy, could be brought in from a great distance by high winds.

### ATMOSPHERIC STUDIES

A research council to study pollen distribution throughout the nation is being set up by the American Academy of Allergy.<sup>81</sup> There will be three major divisions: aero-allergens, foods-drugs, and pharmaceuticals. The first subject to be studied will be airborne substances causing allergies. Subcommittees will deal with pollens, molds, dusts, and miscellaneous allergens. In co-operation with the U. S. Weather Bureau, they will prepare a daily pollen count map that will be offered to newspapers for publication.

Dr. W. C. Jacobs,<sup>80</sup> Weather Bureau Climatologist, reported that the agency is planning to set up a "storm-warning system for hay fever and asthma sufferers" by which it will forecast, twenty-four to forty-eight hours in advance, the arrival of an air mass laden with ragweed pollen in a given area. Southern Indiana is the region having the greatest ragweed pollen density. Air currents carry pollen hundreds, and even thousands, of miles and the climatologists plan to follow these concentrations and map their courses.

Durham,<sup>25,26</sup> continuing his studies on atmospheric allergens, observed that there was a definite variation in the velocity of the fall of pollen grains in a 4-foot column of air. Some of this doubtlessly was due to the difference in the size of the pollen grains. Another factor might be the static changes imparted to the individual granules in their expulsion from the atomizer. As a result of this study, it was evident that some pollens, such as blue grass, Russian thistle, and oak, fell twice as fast as that of common ragweed. A final gravity count of these pollens should be discounted 50 per cent in order to have an approximately correct determination of the number of pollen grains in a given volume of air as compared to common ragweed.

As a result of five seasons of experimentation with various gravity-sampling devices controlled by parallel volumetric tests, Durham<sup>27</sup> stated that air samples should be taken on the unobstructed top of a tall downtown building. He described a sampling device which consisted essentially of two parallel planes of polished stainless steel, with the slide holder raised one inch above the lower plane. He submitted a conversion factor with volumetric conversion of pollen and fungus spore counts, presenting definite factors for about forty pollen and one fungus spore. Two sets of conversion factors were listed, so that counting might be done on the basis of one square centimeter of slide area, or on 3.6 square centimeters.

The National Pollen Survey Committee of the American Academy of Allergy<sup>4</sup> reported acceptance of a sampling apparatus devised by O. C. Durham, and also suggestions for standardization of the common procedures used in pollen counting.

### CHEMISTRY OF POLLEN

Wodehouse and Coca,<sup>115</sup> in their review of the chemistry of pollen antigens, presented the following conclusions: (1) The molecular size of the antigen was large enough to make it nondialyzable through the usual semipermeable membranes, yet small enough to deny a protein character and to indicate that it was a complex

polypeptide. (2) It was resistant to heat and not heat-coagulable. (3) It gave a positive reaction to the biuret test. (4) It was not easily digestible. (5) It was a relatively weak antigen in lower animals, and it appears to be quite identical throughout the grass family. It appeared to be a common antigen in the tall and short ragweed and probably in all the other members of the ragweed family. In all the species of the chenopod-amaranth group which have been studied, there has been found a common antigen. Among the trees, the antigen appeared to have only a generic character, extending sometimes through related genera, and even whole families.

That much confusion still existed in 1946 was evident in the work of Sherman and Stull,<sup>100</sup> H. S. Baldwin et al.,<sup>11</sup> and K. Robbins, M. Mosko and A. Samuels,<sup>79,91</sup> although, in general, many investigators agreed on the chemical characteristics of pollen. The fraction S of Baldwin et al., which was the fourth alcoholic fraction, was negative to both the biuret and ninhydrin test and contained 1.4 per cent nitrogen. The fraction A of Robbins et al. was somewhat similar to fraction I of Cooke and fraction S of Baldwin.

Fraction A of Robbins et al.<sup>79,91</sup> is a heat stable fraction of water extract at pH 4.0 adsorbed on aluminum hydroxide, released by phosphate buffer at pH 7.4, and precipitated by alcohol. They concluded that their substance contained protein and thirteen amino acids were noted. In it there was a carbohydrate polysaccharide, containing hexose, pentose, and hexuronic acid, no hexamine, and 50 per cent protein and 50 per cent carbohydrate. This substance contained a very small amount of flavonal, demonstrated by spectrophotometric analysis, and was a more reactive agent than a whole ragweed solution of the same nitrogen content and total solids in ragweed-sensitive patients. Therefore, it was obvious that this substance, which they claimed was the skin reactive principle, appeared to be a complex protein carbohydrate.

## STANDARDIZATION

Many attempts have been made to standardize pollen; however, there has been little unanimity as to the active principle, or principles. Each method tried eventually has been found to be faulty. Methods, using as a basis weight volume, total nitrogen, and protein nitrogen, have not stood the test of time. This probably was due to the fact that pollen contains more than one antigen. First, a standard method for the preparation must be accepted, then an evaluation of the various antigens can be undertaken. It has been agreed that one method will not solve this problem, but that biologic assay also will have to be done. Elmer Becker<sup>12</sup> reported a method of assaying ragweed pollen by means of the "Quantal" response. This assay was based on one biological property of ragweed pollen extract—the direct skin reactivity. This method of assay was an adaptation of the method of Bliss and consisted of using a number of different dilutions of a given extract and making skin tests on patients specifically sensitive to ragweed. The percentage of positive reactions to each dilution was transformed into probits and the probits plotted against the log of the dose (reciprocal of the dilution). A straight line resulted. The problem of assaying different solutions became the problem of comparing the dose-response curve. This method gave not only the estimate of the ratio of the potencies of two solutions, but an estimate of the error. This method has been validated for scratch test, and its validity for intradermal testing now is being investigated.

George E. Rockwell,<sup>93</sup> chairman of the Standardization Committee of the American College of Allergy, has reported a method of standardization which is a combination of a chemical and biological test. This method has been reported in a recent edition of the *ANNALS OF ALLERGY*. It is by far the most accurate method of standardization of allergenic extracts so far presented.

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### IMMUNITY

Rackemann,<sup>80</sup> Alexander et al,<sup>1</sup> and Cooke did not believe that the concentration of thermostable antibody always was proportional to the degree of clinical relief from symptoms of hay fever, that was the original concept of Loveless, but has not been corroborated. This may be due to the fact that the chemical structure of pollen has not been established.

A direct test for blocking antibody in patients treated for hay fever was reported by K. Maunsell<sup>73</sup> of England. This test detected and titrated the blocking antibody of Cooke, in the patient's skin. The development of a blocking antibody in the serum of subjects specifically treated for hay fever was confirmed by this method. The blocking titer was used as a guide in assaying chemical protection. No blocking antibodies were detected in subjects with hay fever treated with injections of nonspecific human isoserum. Instead of injecting a mixture of isoserum and pollen into non-sensitive skin, the skin of subjects with hay fever was tested with mixtures of their own serum and pollen. Thus, a "direct" blocking test with autoserum was developed.

Alexander, Johnson, and Alexander,<sup>1</sup> reported further studies in measurement of circulating antibodies and antigen. They noted that relief of ragweed hay fever usually was associated with elevated titers of thermostable antibody. However, the titers of thermostable antibody were not directly related to the amount of specific treatment, as there was marked individual variation. During the pollen season, circulating antigen was observed in treated and untreated patients, as well as in normal persons, and it was related to the pollen concentration in the air. From their work, it appeared that the circulating antigen did not cause symptoms and need not be considered in the treatment of hay fever. The values of circulating antigen and thermostable antibody did not correlate with reagin titer. In their experience, perennial treatment gave better results than preseasonal injections.

Mosko and Robbins<sup>79</sup> reported on the immunologic properties of their fraction, which supposedly was specific for the skin reaction in hay fever. The fraction could be injected into patients without producing significant constitutional reaction. It did not shock guinea pigs sensitized to whole ragweed, nor did it sensitize guinea pigs. Combined with gelatin or human gamma globulin, it became more able to produce systemic reaction in patients with natural sensitivity to ragweed, but did not produce shock in guinea pigs sensitive to whole ragweed. The authors thought that treatment with this fraction during the past ragweed season gave evidence of improved therapeutic effectiveness, warranting further studies.

Kulka and Hirsch<sup>64</sup> reported on a study of sensitization to ragweed extract and the production of antibodies by means of adjuvants. In rabbits under observation for two years, they noted variation of the antibody levels following repeated injection of ragweed extract and adjuvants, and the nature of antibodies passively transferred from the guinea pig sensitized to ragweed pollen extract. The rabbits were injected with ragweed pollen extract in water and in oil emulsions containing killed tubercle bacilli, and were observed over a period of two years. Repeated injections produced more vigorous sensitization and antibody formation than did a single injection. Once a maximum serum antibody level was reached, it could not be increased by further injection. In guinea pigs, injected with ragweed pollen extract with adjuvants, there developed antibodies capable of passively sensitizing normal human skin. These antibodies quantitatively were unrelated to colloid agglutinating titer. There was no relation between them and degree of skin sensitivity, or susceptibility to shock. The use of such substances might be of some value in clinical therapy, because of high antibody titer, for control of clinical symptoms.

Samter and Becker,<sup>97</sup> studying nasal secretions for the presence of specific reagins in ragweed-sensitive patients, noted that the nasal secretions of seven of ten patients were positive. Nasal secretions from normal persons were negative. They believed

that these observations might be significant for a better understanding of the clinical course of pollinosis.

Walzer and Golan,<sup>114</sup> reported on a series of experiments, demonstrating that antigen was transported through the body from the positive to the negative pole. It could be introduced into the body at either pole, but was transported only from the positive to the negative pole. It could be transported through more than one person in a relatively short period of time.

## DIAGNOSIS AND SYMPTOMOLOGY

Brown et al<sup>19</sup> reported on a significant study of dyspnea and diminished vital capacity as a symptom and a sign in hay fever. They observed that of thirty-eight pollen-sensitive patients subjected to repeated vital capacity determinations all but twelve showed a diminished vital capacity during the pollen season. Some had asthma as a complication of their hay fever, but were free of asthma at the time the vital capacity measurements were made. They discussed the possibility that diminished vital capacity might represent latent bronchial asthma. In 30 per cent of the patients, the vital capacity was noted to undergo periods of reduction in the absence of any nasal or chest symptoms. In thirty patients, upper respiratory infections were associated with a significant drop in vital capacity.

London<sup>71</sup> reported on an interesting incidence of hay fever in an infant four months of age. Scratch tests were positive to short and giant ragweed and cocklebur. The patient responded to therapy and there has been no recurrence of symptoms since 1942.

Rosen<sup>94</sup> reported on a patient with hay fever followed by asthma, which occurred after maximum exposure to ragweed pollen. This patient was a soldier who previously had lived in an area where there was a much lower count. Prior to that time, he had not had any symptoms and there was no past personal or familial history. During the season, his reactions to skin tests were very large; after the season, they were small.

While in the army, the same author<sup>95</sup> observed 100 men, hospitalized because of asthma, with special reference to nasal and paranasal symptoms and findings. He found that fifty-five had perennial or seasonal nasal symptoms; of ten with seasonal hay fever and asthma, eight had hay fever prior to asthma and the other two had a simultaneous onset. Of fifteen patients with perennial asthma and seasonal hay fever, nine had the onset of asthma and hay fever simultaneously. In two patients, asthma preceded the hay fever, and in four, hay fever antedated the asthma. Examination of the nasal mucosa, by an ear, nose, and throat consultant, revealed positive allergic findings in eight of forty-five patients without nasal symptoms. Transillumination of the sinuses was positive in fourteen of forty-five patients without nasal symptoms and in twenty-three of fifty-five with nasal symptoms. X-rays of the sinuses were positive in twenty-seven of forty-five without nasal symptoms and in twenty-three of fifty-five with symptoms. Intracutaneous tests were positive more frequently in patients with nasal symptoms, especially to the pollens.

Jamieson<sup>59</sup> reported on a patient with asthma due to bee scent who also developed symptoms of hay fever. In *Clinics*, Leo H. Crip,<sup>21</sup> writing on allergic rhinitis, noted that in many patients with nasal allergy there developed obstruction of the eustachian tubes, with labyrinthine vertigo as a secondary manifestation.

## TREATMENT

Specific treatment for hay fever has withstood the test of time. Each year new methods for specific treatment are introduced, but none have been an improvement over the hypodermic method. The use of oral pollen and specific propeptanes of pollen have been given little encouragement in the literature.



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Herrmann<sup>55</sup> discussed the inunction of allergens with "Intraderm." Sufficient clinical improvement in patients with allergy warrants its further study and observation.

Hansel,<sup>51</sup> using very small doses for treatment, reported excellent results. In hay fever patients, Hansel advocated the use of coseasonal therapy with small doses of pollen given intracutaneously. When possible, coseasonal therapy should be preceded by preseasonal treatment. The initial dose was determined by the dilution of extract which caused a 15 mm. wheal following intracutaneous injection. If this size wheal was produced by a 1:100,000 dilution, treatment was started with a .02 ml dose. The amount was increased by .01 ml every two to five days until the optimal dose was reached. In patients with moderate sensitivity it could be .05 ml of a 1:10,000 dilution. Small doses were used subcutaneously, preseasonally. He concluded that small doses of pollen give satisfactory results in the majority of patients.

Rackemann,<sup>87,88</sup> discussing future problems in allergy, stated there were two parts to the treatment of pollinosis: (1) Specificity of the treatment and selection of proper pollen and (2) mechanics and technique of treatment. He was not sure that treatment with a mixture of various pollen extracts was correct. According to him, skin tests, in themselves, were not an accurate criterion of the pollens to which the patient was sensitive. He stated there were too many false positive reactions and too many patients who were clinically sensitive yet showed no skin reaction. The skin test was a test of the skin and might or might not reflect the sensitiveness of the nasal or bronchial mucosa. The point he made was that the clinical history was, after all, the best index of the substances to which the patient was sensitive. He pointed out that some of the so-called late ragweed sensitivity could be mold sensitivity. He stated that specific mold sensitivity was very striking and that, in pollen surveys, local conditions were very important, such as peculiar air currents and backyards. In treatment, much of the difficulty, such as reaction, might be overcome if ragweed antigen could be separated into a skin-sensitizing fraction and an immunizing fraction. So far, no satisfactory method has been developed to accomplish this separation.

### ANTIHISTAMINE DRUGS

Probably the outstanding feature in this year's literature has been the plethora of papers on the use of the antihistamine drugs, benadryl and pyribenzamine. However, it is interesting to note at this point that Loew, Macmillan, and Kaiser<sup>60</sup> reported that, from some experiments on guinea pig serum using benadryl to antagonize histamine and barium and acetylcholine, they noted that benadryl could not be regarded as a specific histamine antagonist.

Benadryl is one of the histamine-neutralizing substances which has received a great deal of publicity and on which some very encouraging clinical reports have been presented.

Logan,<sup>70</sup> reporting on the use of benadryl in allergic diseases of children, stated that his results indicated that the drug was useful if employed in an adequate dosage.

Code,<sup>20</sup> in the Proceedings of the Staff Meetings of the Mayo Clinic, gave a comprehensive review on benadryl as an antihistamine substance, on the antihistamine substances which led to its development, and on its mode of action in anaphylaxis and in allergy. He discussed its mode of action in drying the secretions associated with hay fever and in producing dryness of the mouth. A very excellent bibliography accompanied this report.

Jenkins, Schrieber, and Sheldon<sup>60</sup> reported on the use of benadryl in the treatment of hay fever and asthma. From this, it appeared that it was a valuable adjunct in the control of certain of the hay fever symptoms of grass and ragweed pollen-sensitive patients. Those symptoms were rhinorrhea, itching of the nose,

sneezing, itching and watering of the eyes, and itching of the throat and palate. Nasal obstruction and fatigue which accompany pollinosis frequently are not relieved by this drug. In patients with bronchial asthma due to grass and ragweed pollen, there was significant subjective improvement in only six (26 per cent) of twenty-three patients. Unpleasant reactions to benadryl occurred in 75 per cent of all patients studied. Waldbott,<sup>113</sup> commenting on his clinical results with benadryl, noted that it was of great value in treating infants with asthma. In his series, he had what he classified as complete results in 32 per cent of patients with asthma, 51 per cent complete results in those with hay fever, 43 per cent complete results in the ones with vasomotor rhinitis, and 80 per cent complete results in patients with urticaria. He felt that the action of this drug was most impressive, although by no means ideal because of unpleasant side effects in a large number of patients. He raised the question as to whether or not there might be a spontaneous sensitivity to this drug, due to the fact that three patients suffered asthmatic attacks shortly after ingesting it. His findings would indicate that the drug was more effective on the allergic wheal than on bronchospasm.

Levin,<sup>66</sup> treated seventy-eight hay fever patients with benadryl, some of whom were receiving hyposensitization therapy, although some were not. Fifty-nine per cent of the ones receiving the drug reported good symptomatic relief. Side reactions were less frequent in children. A number of patients were relieved by the drug on certain days and not on others, even though larger doses were taken. (It would have been interesting to have had data as to the pollen counts and opportunities for exposure on those days.) He did not observe any patient with hay fever whose symptoms had been aggravated by benadryl. In some patients, who were given the drug in 100 mg. doses twenty minutes prior to scratch testing, no appreciable influence upon the skin tests was noted.

Of fifty-two patients with hay fever treated with benadryl by Koelsche, Prickman, and Carryer,<sup>61,62</sup> thirty-nine were benefited. Of nineteen with both asthma and hay fever, fourteen patients benefited. In twelve patients with bronchial asthma alone, only four were relieved.

Zolov,<sup>117</sup> commenting on the use of benadryl, stated that it was a powerful new chemical compound which possessed antiallergic activity and beneficial effects might be expected within a few hours after its administration. He observed that the most frequent side effect was dryness of the mouth. However, not infrequently, transitory drowsiness might be alarming. The use of the drug for asthma had not been very encouraging, and he believed that its most successful therapeutic application would be for patients with hay fever, urticaria, and vasomotor rhinitis. Thacker,<sup>110</sup> reporting on its use in seventy-two patients with vasomotor rhinitis, perennial allergic rhinitis, and nasal allergy associated with asthma, noted that complete relief was obtained in 50 per cent of the first, 42.8 per cent of the second, and in 50 per cent of the third group. He concluded, however, that benadryl certainly was not the solution of the allergic problems which face the physician and his patients.

Schwartz and Levin<sup>69</sup> used this preparation in fifty patients with various allergic manifestations and observed that symptomatic relief was obtained in eight of twenty patients with asthma, in six of ten patients with vasomotor rhinitis, in four of five patients with chronic urticaria, in all of eight patients with acute urticaria, and in three of seven patients with miscellaneous allergies. The majority of their patients reported benefit within one hour after administration; symptomatic relief was palliative and side reactions occurred in thirty patients. The side reactions in twenty-six of these patients disappeared gradually, even though administration was continued. The other four stopped the drug, due to the severity of their symptoms.

Eyer mann<sup>37</sup> used benadryl in fifty-two patients with pollinotic vasomotor rhinitis and completely relieved the symptoms in 67 per cent. In 23 per cent of this group,

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the sneezing was relieved, but not the other associated symptoms. In 9 per cent of these patients, no symptoms were relieved. In all patients relieved, the symptoms recurred promptly when the drug was stopped. He stated that the palliative effect in a high percentage of patients with pollinotic vasomotor rhinitis and urticaria would support the hypothesis that histamine or a histamine-like substance was released during an allergic reaction. However, the relief of the symptoms was not conclusive proof that they were due to histamine. The instances in which the itching and sneezing were controlled, but the turgescence of the turbinates was uninfluenced, and the instances of this ineffectiveness in wheezing and dyspnea, suggested that factors other than histamine were responsible for the total clinical picture.

Bowen<sup>16</sup> concluded that benadryl had a true place in allergy and obtained its best effect in patients with chronic urticaria. He also believed it was an excellent aid for patients with allergy due to ragweed and noted improvement in 60 to 70 per cent of such patients. One of five patients had sleepiness as a side effect; however, this was minimized by the administration of caffeine or benzedrine. He felt that benadryl should be used carefully in any aspirin-reactive patient. He stated that the use of benadryl did not exclude thorough allergic investigation and that its place is only as an adjunct in the management of allergic patients. His paper included some unpublished figures which we quote here: Parke, Davis & Co. investigators<sup>83</sup> reported on 404 patients with 82.4 per cent improvement. Derbes reported 70 per cent improvement and Efron, 65 per cent. In patients with the so-called "hay fever x," so frequently encountered in the South, benadryl helped 30 per cent. In contradistinction to such glowing reports, Friedlaender<sup>42</sup> noted no apparent benefit from its use in hay fever and stated that his results suggested that histamine might be a more important factor in urticaria than in other allergic conditions.

In 188 patients, Todd<sup>111</sup> was impressed with the rapidity of action of benadryl and with the full therapeutic effect of relatively small doses on acute manifestations; for chronic conditions more was required. Eleven of his patients suffered from seasonal rhinitis due to pollen and complete relief was obtained in all of them. The chief side effects were: drowsiness, dizziness, dry mouth, and nervousness. They occurred in a considerable percentage of patients using the drug; however, the duration usually was very brief. He cautioned that, although no acquired allergy to the drug had been reported, this possibility must be kept in mind.

Harley<sup>52</sup> treated five patients who were grass pollen-sensitive; three of them obtained prompt and complete relief; one was greatly improved; but the fifth received no benefit.

Stroh<sup>108</sup> recommended benadryl as a palliative treatment until allergic investigation could be made. He believed that its side reactions were far too frequent and unpredictable. Its use was beneficial in controlling itching and also for its sedative action. It was of value for treating hay fever, but failed for acutely aggravated allergic manifestations.

An interesting sidelight on its side effects was reported by Davison,<sup>24</sup> in a letter to the International Correspondence Society of Allergists, in which he noted that benadryl caused the fetal movements to stop after its ingestion by a pregnant woman. The mother became sleepy and apparently her baby went to sleep too. When the drug was stopped, the movements of the child began again and there were no untoward effects.

An anonymous contribution<sup>8</sup> on the subject of benadryl appeared in the *American Professional Pharmacists*, in which it was stated that benadryl seemed to be a potent antihistamine agent, although the mechanism of its action was not understood fully. Its action in drying the secretions accompanying hay fever and in producing dryness of the mouth might be due to blocking of the secretagogue action of histamine. The shrinking of the mucous membrane and the disappearance of wheals might be due to its antihistamine effect on blood vessels.

Friedlaender and Feinberg<sup>14</sup> reported that the local application of benadryl exerted a marked reduction in the whealing reaction in ragweed-sensitive subjects. This would suggest that histamine, or a histamine-like substance, plays a role in the promotion of the wheals. They stated that the action of the drug was thought to be produced by displacement of histamine from its site of action. It was suggested that its failure when administered orally to affect materially certain types of allergy, in which histamine was thought to play a role, might be the result of insufficient drug reaching the site of action.

It might be well at this point to note that, in the October, 1946, issue of Parke, Davis and Company's<sup>83</sup> *Therapeutic Notes*, there was a summary on the histamine concept of allergy, and a review of the literature on benadryl, its pharmacology, clinical use, dosage, and side reactions.

Another histamine antagonist which, from published and many unpublished reports, has appeared to be even more effective than benadryl, both from the therapeutic standpoint and because of a lower incidence of side effects, is pyribenzamine.

In his article, Epstein<sup>36</sup> presented the conclusion that pyribenzamine and benadryl were very efficacious in the symptomatic treatment of patients with urticaria and hay fever and, to a lesser extent, those with perennial rhinitis, asthma, atopic dermatitis, and other forms of allergy. He believed that there was not much difference between the two drugs in their clinical efficacy, and quoted the following percentages of relief obtained—95 per cent in patients with acute urticaria, 80 per cent in those with chronic urticaria, 80 per cent in patients with hay fever and extrinsic allergic rhinitis, and about 40 to 50 per cent in those with bronchial asthma. He further stated that their usefulness is limited, since they exert only a symptomatic effect. However, as he pointed out, such relief might equal a clinical cure in self-limited allergies, such as attacks of acute urticaria, drug eruptions, or hay fever. He noted that they were of low toxicity when given orally and were tolerated well. He cautioned, however, that the natural limitation of these drugs should be kept in mind and that we should not be overoptimistic.

Feinberg,<sup>39</sup> writing on histamine antagonists, summarized his presentation by stating that, even at that early stage of experimentation, it was evident that the use of benadryl and pyribenzamine would be limited because they would not be effective in many of the manifestations of allergy and because of toxicity and undesirable reactions. Further limitation was of course evident from the fact that, at best, such remedies were only palliative and did not produce any lasting benefit.

In an editorial<sup>29</sup> in the *ANNALS OF ALLERGY*, there was presented a brief critique of the newer antihistamine drugs, as well as some pertinent statements on histamine. It was stated that, although these antihistamine drugs undoubtedly relieved a certain percentage of hay fever patients, they did not offer any cure or hope of cure when used alone. It was interesting to note at that point that hay fever patients with mild symptoms also were often relieved by sedatives, hot drinks, or rest. Seven patients with hay fever benefited very little from antihistamine drugs. Large doses were apt to cause side reactions in many instances. In the editorial it was stated further that if wheal formation took place on cutaneous testing, a good response to benadryl or pyribenzamine might occur, but erythematous reaction to skin tests usually pointed to failure when these drugs were employed. Most patients with mild and moderate hay fever responded to specific immunization procedures, but in patients with more severe allergy there was a fairly large number of failures. The antihistamine drugs did not fill this gap. One ray of hope could be offered—a combination of these two forms of therapy. In many patients, who were very sensitive to ragweed pollen and were unable to receive a sufficiently high dose of pollen extract without reaction, the reaction could be controlled with benadryl or pyribenzamine. The author of the editorial believed, however, that it was too soon to make a proper evaluation of these drugs.

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There were further comments in this same journal on the subject of benadryl,<sup>33</sup> that the clinical evaluation of this drug as an antihistamine compound was open to serious question. No doubt it had a useful place in medicine as an adjuvant measure, but where this usefulness would be had to be determined. In the editorial was brought out the fact that there was a strong sedative reaction with this drug, which should be viewed as a primary rather than a side reaction, and that adequate control studies, using narcotics, sedatives, or hypnotics which produce drowsiness in approximately 50 per cent of the patients, should be used for comparison of their effect on patients with asthma, hay fever, and urticaria.

An editorial<sup>35</sup> worthy of note appeared in *Medical Times* in which were reviewed some pertinent facts on histamine and its possible relation to allergy. There was a summary of the use of benadryl as an antihistaminic, its toxic reactions, and possible mechanism of action and the conclusion was presented that the results reported on this drug left little doubt that it, or some other like it, would have a definite place in therapy.

Feinberg<sup>38</sup> presented a masterful review of histamine and antihistamine agents, in which he stated that benadryl and pyribenzamine were useful symptomatic remedies in the treatment of seasonal hay fever. He felt that their order of effectiveness was pyribenzamine, neoantergan, and benadryl. Both pyribenzamine and benadryl caused a high incidence of side reactions, among which sedation and drowsiness were most common; these reactions were more frequent and of greater intensity with benadryl. In the use of these agents, the following should be considered: (1) A cure or lasting improvement was not to be anticipated. (2) At best, they exerted a temporary palliative action. (3) Many patients would fail to respond to them. Specific allergic methods should not be abandoned, as at that time they were the sole means of achieving lasting results. Another fact to be kept in mind was that the remote toxicity, in contradistinction to the immediate reaction, had not been studied sufficiently up to that time. To the best of his knowledge, these drugs acted by competing with the liberated histamine in their attachment to the receptor cell. Therefore, the benefit was only symptomatic and lasted for only a few hours after each dose. It was important to keep in mind the possibility that, while the patient was being helped temporarily by one or the other of these drugs, the long term program of creating immunity might be interrupted by this same drug if it was noted that they interfered with desensitization.

In *The Journal of Allergy*, in an editorial<sup>34</sup> on the subject of histamine antagonists, it was stated that patients in the acute sneezing and coryza stages of hay fever were influenced favorably by benadryl and pyribenzamine, but those with the congestive nasal obstruction of the later stages of hay fever or perennial vasomotor rhinitis were relieved to a much lesser extent. In patients with these types of allergy, pyribenzamine produced a more favorable response. The pollen-sensitive patients with asthma, who neglect their desensitization program because of their reliance on these drugs, will be disappointed greatly. The side effects of these drugs were becoming increasingly evident. Benadryl produced a marked soporific effect in a high percentage of patients. Disregard for this particular action and the resulting lack of alertness in the person might lead to accidents. Pyribenzamine had a similar action, but to a much lesser degree and less frequently. It had, however, other toxic actions. One of the most frequent was an excitatory effect consisting of nervousness, tremor, tachycardia, weakness, and insomnia. Not infrequently, a combination of sedation and stimulation was observed. At times, inability to concentrate and mild mental confusion occurred. Anorexia and gastric discomfort also might develop. Benadryl might also produce any of these symptoms. At best, these remedies were only palliative, a fact which should be emphasized to the patient. Unless this was continually observed, great harm could be done by dis-

ruption of desensitization programs. Many types or phases of allergic phenomenon were not relieved by these compounds. A very important fact was pointed out, that more prolonged and more extensive observation might disclose more intense or delayed toxic action of these drugs. Extensive experimentation with these and new synthetic compounds was in progress, and this search might yield more basic remedies.

An editorial<sup>32</sup> appeared in the *Canadian Medical Association Journal* presenting a summary of the Mayo Clinic reports. From this it would appear that benadryl prevented at least some of the pharmacologic actions of histamine, and was particularly effective in allergic patients when the underlying problem was edema provoked by release of histamine or histamine-like substances. Dramatic relief of symptoms occurred in patients with urticaria. However, the results were much less striking in hay fever. The side effects reported with significant frequency were sleepiness, dizziness, dry mouth, and nervousness.

Mayer et al,<sup>76</sup> investigating the toxicity of pyribenzamine, reported that six human beings tolerated up to 500 mg. of this drug daily, given in 100 mg. tablets. Mild sedation in one and mild nausea with "pelvic heaviness" in another of these subjects were the only untoward symptoms. The toxicity and antihistamine action of pyribenzamine were such that extended investigations were warranted.

In another article, Mayer<sup>75</sup> gave a good discussion of some antihistamine substances, including their chemistry, antihistamine activity *in vitro* and *in vivo*, their effect on anaphylaxis in guinea pigs and in dogs, and some thoughts on their mechanism of action.

Arbesman, Koepf, and Miller,<sup>70</sup> reporting on some of the properties of pyribenzamine, noted that it had potent antianaphylactic activity demonstrated by passive anaphylactic experiments in guinea pigs. When administered orally to human beings, there was a decrease in the size of histamine skin wheals in eighteen of twenty-eight patients. The skin reactivity of fourteen of twenty-four allergic patients diminished following oral administration of this drug. In September, the Committee on Pharmacaceuticals and Medicaments of the American Academy of Allergy,<sup>6</sup> stated that it seems obvious that pyribenzamine was a useful palliative drug for certain allergic diseases, such as acute vasomotor rhinitis, seasonal and nonseasonal, and acute urticaria. It appeared to be less effective for the relief of asthma and dermatitis. They stated further that it would take a longer time to make a final evaluation of this drug, but it seemed safe to say that at that time it was very useful for symptomatic control. There was some indication that tolerance might be established if it was used over a long period of time; it was not a cure for allergic diseases.

Arbesman, Koepf, and Lenzer<sup>9</sup> made clinical studies with this drug on 495 patients. It relieved sneezing, rhinorrhea, and nasal occlusion in 75 per cent of 313 patients with allergic rhinitis. Results were better in patients with seasonal pollinosis than in patients with the perennial, so-called extrinsic or intrinsic type. They noted that it was apparently harmless in effective doses, but had some undesirable, although not serious, side effects. In eight patients, 100 mg. of pyribenzamine, one half hour prior to treatment, was capable of preventing constitutional reactions which ordinarily would occur with that dose.

Koepf, Arbesman, and Munafo,<sup>63</sup> studying the effects of chronic toxicity of the drug, observed no effect on the general behavior of dogs to whom they had administered 50 to 100 mg. daily for a prolonged period (one year). Hematopoiesis was not altered in these animals, nor did the drug produce a febrile reaction or impair liver or kidney function. In three human beings who were given 150 mg. of pyribenzamine daily for eighty days, no chronic toxic changes were noted. They noted, however, that such limited studies on human beings were not sufficient to warrant considering the drug completely harmless.

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Friedlaender and Friedlaender<sup>45</sup> used pyribenzamine for various types of allergic disorders and noted that it afforded symptomatic relief in many patients with seasonal hay fever, perennial allergic rhinitis, and urticaria. Its action on asthma was negligible. Side effects, consisting of drowsiness, gastrointestinal upsets, and vertigo, occurred in 27.2 per cent of their patients. They felt that it was a valuable symptomatic drug for use as an adjunct to specific therapy.

Our own experiences with benadryl and pyribenzamine would, in general, seem to be similar to the ones previously mentioned. We have noted that pyribenzamine has been more effective, both from a therapeutic standpoint and from the standpoint of less frequency of unpleasant side effects. It would be apt at this point to state, as Feinberg did, that it is hoped that the advent of this type of therapy will not cloud the issue, nor dampen the ardor of our search for information of more basic value, that will help us to understand the mechanism of the allergic reaction and the constitutional background of allergy and find means for the connection of both.

### OTHER THERAPEUTIC AGENTS

A few articles on other therapeutic agents were published this year.

Meier and Bucher,<sup>77</sup> reporting on antistine, a new synthetic antihistamine substance, stated that its specific effect is its antagonism to histamine. In their experiments with animals they found that when applied locally as well as generally, it had an antihistamine action. They found that when it was applied locally in experimentally-produced conjunctivitis, it produced noticeable improvement. The preparation also proved effective in anaphylactic conditions. In another article they presented their observations on the influence of antistine on antibody production, and concluded that it did not inhibit the antibody production stimulated by repeated antigen injections. In fact, antibody production was increased in these animals; perhaps, as they suggested, because of the protection given by antistine allowing the animals to tolerate a much larger amount of antigen.

Bourquin<sup>17</sup> found that antistine was of great value, since it gave relief to many patients suffering from hay fever. Because of its low toxicity, he recommended it for all allergic conditions of the eye.

Schindler<sup>98</sup> used antistine in thirty-nine patients with allergic conditions, at the Medical Clinic of the University of Basel. Ten of these patients had bronchial asthma and eleven had urticaria, none apparently were hay fever patients. He found the therapeutic effect to have been very good for urticaria, and good for some patients with asthma. The average daily oral dose was 300 mg., but 600 mg. also has been tolerated. Subcutaneous and intravenous methods of administration also were used.

Feinstone, Williams, and Rubin<sup>40</sup> introduced a new antihistamine drug, hetramine, and its activity was demonstrated in laboratory animals. They felt that this drug might have a beneficial effect on some of the varied symptoms associated with hypersensitivity. Clinical trials are being conducted now in a variety of conditions including hay fever, urticaria, and physical allergy.

Loew, Kaiser, and Anderson<sup>68</sup> reported on the antihistamine action of five alkyl-oxy-triazines in guinea pigs, and noted that they were two to ten times as effective as aminophyllin.

An article by Ghiselin,<sup>46</sup> on the use of anthallan, received some publicity in the East. His study was conducted on forty-two patients with seasonal and nonseasonal hyperesthetic rhinitis.

At the start of treatment, the patients had suffered from their disease for an average time of 506 days (from eleven days to five years). With the customary methods of treatment, they had had only short periods of relief. In forty out of

forty-four (90 per cent) courses of treatment with anthallan, a beneficial influence of the drug was observed. The improvement varied between 25 and 100 per cent subjectively and objectively, as evaluated by an arbitrary schedule of numerical ratings of all the subjective and objective manifestations involved. The persistence of improvement was observed for an average of fifty days (7 to 248 days). Laboratory studies and examinations did not indicate any harmful effect of treatment with anthallan. He concluded that anthallan in doses of three to twelve capsules daily was a useful drug for obtaining relief in a high percentage of patients with seasonal and nonseasonal hyperesthetic rhinitis and that it could be used with complete safety.

In an editorial<sup>31</sup> in the *Journal of the American Medical Association*, there were comments on this article, stating that it was difficult to appraise the effectiveness of anthallan from the treatment of forty-two patients who formed the clinical material of this report. In the editorial, it was stated further that the author attempted to evaluate results by a complicated system of assigning numerical values to the symptoms of the patients, averaging them and comparing them with similar averages derived from numerical values assigned at the end of treatment. Because of such statistical manipulations, scientific appraisal of the effects of this drug based on this report was difficult. Also, the study did not include controls, so more scientifically controlled investigations certainly were indicated.

An article on the use of hapamine appeared, in which Eden<sup>28</sup> reported successful treatment of seventeen children with allergic rhinitis, with this preparation. Except in one instance from which one might deduct that the patient was sensitive to spring and fall pollen in addition to other substances, the details of the sensitivities of the patients were not given.

A report of the Committee of Pharmaceuticals and Medicaments of the American Academy of Allergy,<sup>5</sup> presented this year, recommended the removal of torantil and hapamine advertisements from *The Journal of Allergy*.

Following local anaesthesia, Dimov<sup>23</sup> injected a 10 per cent solution of calcium glucono-glacto-gluconate into the submucosa at the base of both inferior nasal turbinates of patients with allergic rhinitis. Hardening of the turbinates occurred with sclerosis. Sneezing, rhinorrhea, and itching were relieved in some patients after the first injection, and development of polypi was prevented. About 90 per cent improvement was obtained.

An article on ethylene disulphonate appeared, in which Blumenthal<sup>14</sup> reported on treating eighteen patients with three injections a week, twelve of whom had asthma and six had allergic rhinitis. The results were negative.

It is interesting to include here the report of the Council on Pharmacy and Chemistry<sup>7</sup> which presented the conclusion that, from a review of the published reports, the statement of the AMA chemical laboratory, and the reports received from physicians investigating the use of ethylene disulphonate in the treatment of various allergic conditions, not only was it evident that the existence of such a compound was open to serious doubt, but that the theory of its dilution and supposed part as an oxidation catalyst of carbohydrate metabolism was based on flimsy biochemical conjectures that had no proven connection with the mechanism of allergy, if indeed there was any. Examination of the product indicated that, by ordinary tests, it cannot be distinguished from distilled water, and the council declared it was not acceptable for inclusion in N.N.R.

## MISCELLANEOUS

Gutmann<sup>40</sup> stressed the importance of history taking in patients with allergic disease, stated that it often led to an explanation even without tests, and cited a number of instances by giving case histories.

Squier<sup>106</sup> also stressed the importance of a complete history, stating that such a



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history provided data of inestimable value in etiologic diagnosis. He noted that clinical sensitivity might be present in spite of negative skin tests. The converse also was true. Skin test information must be correlated with the history and clinical observations. In specific management, avoidance of contact with causal agents and specific hyposensitization were the two fundamental principles. Squier and Rackemann pointed out that, in hyposensitization, caution must be exercised against exceeding the threshold of attained tolerance; overtreatment must be avoided.

Stiles and Johnston,<sup>107</sup> in a study of the inheritance of respiratory allergies, traced a family for five generations and 232 people. The incidence of allergies was 23.4 per cent as compared to 7 per cent in the general population. The specific sensitivity did not appear to be inherited, but rather the capacity, or predisposition, to become hypersensitive. From their data they suggested that respiratory allergy might be interpreted as an irregular dominant characteristic.

Rittwagen, Romano, and Svigals,<sup>90</sup> studying 100 children with rheumatic fever, noted a definitely higher incidence of allergy in the rheumatic patients and in their families. The most frequent allergy was seasonal hay fever.

Hulett<sup>56</sup> reported a screening test for the identification of allergic states that he felt was safe and reliable. He used histamine hydrochloride and injected 1/20 c.c. of 1:100,000, 1:10,000, and 1:1,000 dilutions.

Mausmann<sup>74</sup> felt that the eosinophilic response was used very little; and yet contained much information. Every patient with a nasal secretion, whether acute or chronic, should have a nasal smear.

Dutton,<sup>27</sup> in discussing nasal and sputum smears, stated that the failure to use this valuable procedure was perhaps technical or because of attempting to draw conclusions from inadequately obtained material or too few observations. He stated that the test must be repeated before conclusive evidence could be drawn.

Santer<sup>96</sup> made some interesting experimental studies on eosinophils. Normal saline, histamine in various concentrations, and specific antigen were introduced by spray into the nasal cavity of 198 unselected patients with pollinosis, prior to and during the season. Secretory response (amount and consistency), eosinophilic response, and peripheral eosinophil count were recorded.

1. No parallelism was found to exist between secretory and eosinophilic response.
2. The secretory response, though distinctly exaggerated in most patients with latent nasal allergy, was nonspecific; the eosinophilic response was specific, but only a fraction of the patients responded to introduction of specific antigen, prior to the season, with nasal eosinophilia.
3. Evidence was presented, however, that histamine might be an important exception to this rule; significant differences were noted in the eosinophilic response of patients to histamine administration, prior to and during the ragweed season.
4. Neither secretory nor eosinophilic response obtained prior to the season permitted any prediction of the clinical course.

Hayden<sup>54</sup> reported chromidrosis occurring in a patient with ragweed pollinosis, which developed while she was receiving ragweed hyposensitization and recurred each year for several years.

Parsons<sup>84</sup> reported the use of the sedimentation rate as a diagnostic aid in allergy. In all his hay fever patients, the sedimentation rate was normal. He concluded that many patients with hypersensitivity had complicating diseases which are not of an allergic nature.

Troescher, Ancona, and Kerr<sup>112</sup> found a histamine-like substance present in nasal secretions of the common cold and allergic rhinitis. A method for extraction of this substance was described. There was no striking difference in total histamine activity in the two conditions. There was no apparent correlation between the number of eosinophiles and amount of histamine present in the nasal secretion.

## NEW BOOKS AND REVIEWS

A number of excellent books have been published this year, in which pollinosis is discussed.

Feinberg's<sup>121</sup> second edition, "Allergy in Practice," is a very comprehensive textbook. This edition contains a chapter on histamine in anaphylaxis and allergy by Carl Dragstedt and a chapter on histamine antagonists.

Urbach and Gottlieb's<sup>125</sup> second edition of "Allergy" is probably the most complete reference book on allergy ever published.

The new text by Robert Cooke<sup>118</sup> contains much to be digested and much original work on the subject of the chemistry and immunity of pollinosis. An excellent chapter on immunochemistry is presented.

Volume 5 of "The Clinics," "Therapy in Allergy"<sup>122</sup> is a comprehensive survey of the subject of pollinosis.

Gay's<sup>123</sup> "The Diagnosis and Treatment of Bronchial Asthma" contains the author's concept of the treatment of pollinosis.

Derbes and Englehardt's<sup>120</sup> "Treatment of Bronchial Asthma" contains many excellent chapters on pollinosis.

Two popular books have appeared this year which include a discussion of this subject: "What You Don't Know May Hurt You," by Rudolph and Rose,<sup>124</sup> and "It's an Allergy," by Frank G. Crandall, Jr.<sup>119</sup> This type of book gives much information to the sufferer, but also leads to many erroneous conclusions and well intended misinformation.

Among the excellent reviews appearing are those of Rackemann,<sup>87,88</sup> Hansel,<sup>50</sup> Macquiddy and King,<sup>72</sup> and Rockwell.<sup>93</sup>

A popular concept of hay fever, "Fact and Fiction," is discussed by Fleming.<sup>41</sup>

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## The Use of Intravenous Ethyl Alcohol

(Continued from Page 195)

quent, complete report. The present preliminary notes, it is hoped, will stimulate further investigation by other workers in this field.

Subsequent to the writing of this paper, the treatment has been used on twenty-six patients with similar results. Dr. John D. Gillaspie of Boulder, Colorado, who accidentally discovered the same treatment, reported to the members of the Mississippi Valley Regional Postgraduate Course that he had noted the same effects when ethyl alcohol was given intravenously to five patients with severe bronchial asthma.

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# News Items

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## LOS ANGELES SOCIETY OF ALLERGY

A new allergy organization has been formed in Los Angeles County, under the name of Los Angeles Society of Allergy, as a section of the Los Angeles County Medical Association.

The following officers were elected for the year 1947: President, Dr. George Piness, Los Angeles; vice president, Dr. Willard S. Small, Pasadena; secretary-treasurer, Dr. Frank G. Crandall, Jr., Los Angeles. There is a Council of four members who, with the officers, constitute an Executive Council.

Members of the Los Angeles Society of Allergy must be members, in good standing, of the Los Angeles County Medical Association. The organization is composed of active and associate members. The active members must be certified diplomates in one, or more, of the following: (a) The American Board of Internal Medicine—subspecialty allergy, (b) The American Board of Pediatrics—subspecialty allergy, or (c) The American Board for the Certification of Allergists—or a Fellow or Member of the American Academy of Allergy, or a Fellow or Member of the American College of Allergists. Associate members are physicians in Los Angeles County Medical Association, who are interested in allergy or practice allergy but, otherwise, do not fulfill the qualifications required for active membership.

It is planned to hold four regular meetings each year and any special meetings which may be required.

Under the auspices of the Los Angeles Society of Allergy, a committee composed of Drs. Piness, Small, Hyman Miller, and Lyle C. Bacon, has proposed a fee schedule for the diagnosis and treatment of allergy patients under the medical care program of the California Physicians' Service and the Veterans Administration. Leading allergists in other areas in California have been contacted, and it is planned to hold a conference at San Francisco in the near future with the executives of the California Physicians' Service and Veterans Administration to discuss and, if possible, secure approval of the fee schedule proposed for this state.

## RESEARCH AWARD OF THE AMERICAN PHARMACEUTICAL MANUFACTURERS' ASSOCIATION

Dr. Bernardo Alberto Houssay, of Buenos Aires, was the recipient of the first annual Research Award of the American Pharmaceutical Manufacturers' Association. He received this award in person at Boca Raton, Florida, on April 28, at the fortieth annual meeting of the Association.

Doctor Houssay, who until recently was Professor of Physiology at the Medical School of the University of Buenos Aires, is an authority on the interrelationship of the various hormones. It was through his work that the relation of the pituitary gland to diabetes was firmly established.

In recognition of his work, Doctor Houssay also has received many honorary degrees, including medical degrees from Asuncion University in Paraguay, the Medical School of the Catholic University of Santiago, Chile, and the Medical School in Paris. The University of Toronto awarded him the 1945 "Charles Micle" prize for his work in medicine.

In this country, Harvard University conferred on Doctor Houssay an honorary degree of Doctor of Science. He was honored similarly by the Medical School of the University of São Paulo, Brazil.

Doctor Houssay is a former president of the Medical Academy at Buenos Aires

## NEWS ITEMS

and is a member of many other medical academies, including those of Rio de Janeiro, Madrid, Mexico, and Lombardy, and of the Royal Society of Edinburgh. He is an honorary member of the American Academy of Arts and Sciences in Boston, the Physiological Society of Great Britain, and the American Physiological Society, and is a member of the Harvey Society of New York. He is an officer of the Order of Leopold and an officer of the Legion of Honor.

### NORTHERN CALIFORNIA ALLERGY SOCIETY

On April 23, about twenty allergists from San Francisco and the East Bay region (Oakland) met and officially organized the Northern California Allergy Society.

The Nominating Committee selected the following officers: President, Dr. Albert Rowe, Oakland; vice president, Dr. Samuel Hurwitz, San Francisco; secretary-treasurer, Dr. Minnola Stallings, San Francisco.

Dr. Milton M. Hartman, San Francisco, was authorized to prepare a summary of recommendations and observations relative to the fee schedule for the diagnosis and treatment of allergy patients, which could be presented to the Veterans Administration and sickness insurance organizations. This summary also is being presented before the California State Medical Association convention in May.

### CENTRAL PENNSYLVANIA ALLERGY SOCIETY

The Spring Session of the Forum of Allergy of the Central Pennsylvania Allergy Society was held in Reading, Pennsylvania, on Wednesday, March 26. The meeting was attended by a large and enthusiastic group.

Among the notable physicians who appeared on the program were Dr. Harold Abramson who spoke on "The Present Status of Allergy," Dr. Bela Schick who read a paper on "The Allergic Child and the General Practitioner," and Dr. Carroll Wright who presented "Treatment of Various Allergic Dermatoses."

Dr. Ralph M. Mulligan, secretary-treasurer of this Society, has compiled a booklet, *Thirty Questions and the Allergist*, which gives authoritative answers to questions asked by physicians, who do not specialize in allergy, and their patients.

### SOUTHWEST ALLERGY FORUM

The meeting of the Southwest Allergy Forum was held on March 31 and April 1 at the Washington-Youree Hotel, Shreveport, Louisiana. Over 100 men from eighteen states attended.

The following officers were elected: President, Dr. Herbert Rinkel, Kansas City, Missouri; vice president, Dr. Sim Hulsey, Fort Worth, Texas; secretary, Dr. Fannie Lou Leney, Oklahoma City, Oklahoma. Dr. Carroll Pounders and Dr. Nesbitt Miller, both of Oklahoma City, were elected to the Board.

The 1948 session will be held in Oklahoma City at Easter time, and in 1949 the meeting will be in El Paso, Texas.

### NAVAL AIR RESERVE TRAINING COMMAND

The following notice has been received from the Naval Air Reserve Training Command:

"The Naval Air Reserve Training Command, with headquarters at Naval Air Station, Glenview, Ill., has 17 nationally located Naval Air Stations and 4 Naval Air Reserve Training Units at which Naval Reserve Medical Officers may serve on active duty with full pay and allowances and with the privilege of returning to civilian life at any time upon request. Additional details may be obtained from Chief of Naval Air Reserve Training, Naval Air Station, Glenview, Illinois."



## NEWS ITEMS

### SOCIEDAD MEXICANA DE ALERGISTAS

In a letter dated March 29, Dr. Mario Salazar Mallen, of Mexico City, writes that a Sociedad Mexicana de Alergistas has been founded and has started its activities by giving a short course in allergy in Tampico, Mexico.

Doctor Salazar Mallen, who is president of this new society, states that one of the aims of the society is to maintain cordial relations with similar societies and asks that greetings be extended to the members of the American College of Allergists.

The College extends congratulations and welcome to the Sociedad Mexicana de Alergistas.

### CUBAN SOCIETY OF DERMATOLOGY AND SYPHILOLOGY

For the year 1947, the following members have been elected to the Board of Directors of the Cuban Society of Dermatology and Syphilology: President, Dr. Jorge Pina; vice president, Dr. Pastor Fariñas; secretary, Dr. Guillermo González Peris; vice secretary, Dr. Luis Rodríguez Plasencia; treasurer, Dr. Federico Ordetz; and vice treasurer, Dr. Carlos Castaneda.

\* \* \*

Miss Julia Garcia Games has opened an office in Santiago de Chile, for the purpose of supplying "rapid and correct information" on literary and scientific publications which appear in Latin America.

At the present time, Miss Garcia Games can supply any editorial which is published in Argentina, Uruguay, and Chile. She expects soon to include Peru, Bolivia, and the other countries in South America in this list. She will also furnish catalogs listing the literature of the following fields: poetry, stories, novels, theatre, art, history, law, social sciences, pedagogy, et cetera.

Orders will be taken care of by regular mail or airmail, as desired, and the charge will be figured accordingly.

Inquiries should be addressed to Miss Julia Garcia Games, Casilla 1091, Santiago de Chile, Chile.

\* \* \*

Dr. James Eugene Stroh of Seattle, Washington, has received an appointment as Clinical Professor of Medicine at the University of Washington. Doctor Stroh will maintain his status of Chief of the Allergy Department at the King County Hospital.

\* \* \*

### Correction

A news item in the November-December issue of the ANNALS contained a list of countries in which the national allergy societies officially had become members of the International Association of Allergists. Through error, Denmark was included in this list.

## **Dependable Clean Dried Hayfever Pollens of All Kinds**

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# ANNALS of ALLERGY

*Published by the  
American College of Allergists*

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Volume 5

July-August, 1947

Number 4

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## STANDARDIZATION OF POLLEN EXTRACTS

ROGER P. WODEHOUSE, PH.D.  
Pearl River, New York

### THE METHOD

THE potency of a pollen extract may be determined in terms of standard pollen units, by the following method:

*Standard Pollen.*—A stated amount of pollen, known to have been collected properly from several widely scattered sources, correctly identified, and to be practically pure, is desiccated completely and stored in air-tight containers, as the standard of reference. It is designated as the Standard Pollen of assigned number for its species and year of collection.

*Perpetuation of the Standard Pollen.*—Since it has not been proved that pollen, prepared and kept according to the above-mentioned method, maintains its potency perpetually and since dwindling from use is inevitable, the standard pollen is to be restored each year by withdrawing 25 per cent of it, including that which has been used, and replacing it with an equal amount of fresh pollen. The fresh pollen shall be of the same species, collected from several different sources at the last flowering season and shown to be of the same or greater potency than the standard of the previous year. The mixture of the two batches of pollen then becomes the current standard and is so designated by a new number. The unused pollen that is withdrawn is kept for testing at a future date for possible deterioration.

*Preparation of Standard Extracts.*—Weigh out 2 gm. of fat-free and completely desiccated standard pollen. Extract in 20 c.c. of Coca's solution for twenty-four hours with occasional shaking at 5 to 10° C.

Filter off the extract through Whatman No. 2 filter paper, 7 cm. diameter, with suction. Measure the volume and restore it to 20 c.c. by flowing the

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Dr. Wodehouse is an Associate Fellow of the American College of Allergists.

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necessary amount of Coca's solution over the filter cake and continuing the filtration.

Allow the filtrate to stand seven days at 5 to 10° C.

Sterilize by filtration with diminished pressure through a Seitz (Republic Filter, Inc.) filter pad, Serum No. 1 sterilizing, size No. 3 (35 mm. diameter) used in Seitz filter, improved laboratory model, Size A.

Withdraw a sample for Kjeldahl nitrogen determination and immediately add to the remainder an equal volume of sterile glycerine. Prove sterility.

Calculate the number of nitrogen units per cubic centimeter (0.00001 mg. nitrogen=1 standard pollen unit). The extract is suitable for purposes of standardization for one year if kept without dilution in air-tight containers at 5 to 10° C. It is designated the *Standard Extract* for the species of pollen from which it was made and bears the number of the standard pollen followed by the number of the extraction.

Its potency is stated in terms of *standard nitrogen units* per cubic centimeter, separately determined for each Standard Extract. To this extent the standardization is chemical. Extracts prepared for diagnostic and therapeutic use are assayed on their physiologic activity, regardless of their nitrogen content which need not be known.

The physiologic measure of the potency of a pollen extract is deemed to be its ability to neutralize the homologous reagin of human serum. Standardization of extracts is done by comparing their reagin-neutralizing capacity with that of the standard extract at comparable sites on the same recipient. Their potency is expressed in terms of the standard nitrogen units of corresponding activity, not of their own.

To this extent the standardization is physiologic. Although expressed in terms of nitrogen units, it actually is a measure of reagin neutralization capacity and, as applied to the working extracts, the unit thus becomes a reagin-neutralizing unit.

*The Serum.*—The serum must be from a donor known to be skin-sensitive to the pollen to be tested. It is desirable that the serum be as highly reaginic as possible to permit dilution at the time of use and because there is evidence that the more highly sensitive serums permit more accurate comparisons.

*Dilution of the Serum.*—The concentration of the serum and antigens used in the test must be adjusted to give a suitable range of reactions, since neither excessively small reactions nor those approaching the limits of the recipient's response are suitable for accurate comparisons. The object is to find the concentration of serum which, as it is completely neutralized at a sensitized site, gives a reaction below, but not far below, the limit of response of the average recipient. This may be done by *in vivo* or *in vitro* neutralization of serum dilutions by the standard pollen antigen solution at constant strength.

*In Vivo Neutralization.*—The serum is diluted with normal saline solution without preservative in a series progressing by an arbitrarily chosen common ratio. The choice of ratio depends upon the sensitivity of the serum and the number of sites to be used in the test. Only the most sensitive serums will sensitize in dilutions beyond 1:1,000, and useful dilutions seldom are found beyond 1:500. Consequently, unless the serum is known to be unusually sensitive, about 1:500 is set as the lower limit of the trial dilutions. If six sites are to be used in the trial, the common ratio of 3.5x is satisfactory giving the dilution series, 1:1,\* 1:3.5, 1:12.25, 1:43, 1:150 and 1:525. Six sites are *sensitized* with these six serum dilutions by injecting endermally 0.05 c.c. of each.

After twenty-four hours or longer, each site is *tested* by injecting it with 0.01 c.c. of standard pollen extract of selected concentration (about 100 units per cubic centimeter). The average diameter of the wheals of the reactions and of the erythemas including the wheals are measured and recorded. If co-ordinately plotted in terms of cutaneous reaction units,† these may show the vanishing dilution of the serum and the reaction ceiling for the antigen concentration used.

Twenty-four hours later the sites are *retested* for their residual sensitization with a solution of the standard antigen five or more times as strong as that used in the first test. The weakest concentration of serum to give a reaction on the retest is regarded as the neutralization point of the serum for one-fifth of its volume of the selected concentration of pollen extract. Due to the large common ratio (3.5x) necessarily used for the dilution series in the first trial, this figure for the neutralization point is only approximate. It may, however, be used as the lower limit of concentration to narrow the range of dilutions for the next trial.

*In Vitro Neutralization.*‡—Dilutions of the serum are made as before. Each, then, is combined with an equal volume of 100-unit standard pollen extract and the mixtures are allowed to stand at room temperature for one-half hour. This time-lapse is introduced here merely for convenience in assembling materials and preparing the recipient and has no other significance. However, there is evidence of some deterioration in the diluted antigen even in this short time, hence the time-lapse must be standard procedure.

Six sites are prepared by injecting them with a chosen amount (0.05 to 0.1 c.c.) of each of the serum-antigen combinations. Though these injections are really tests, as well as sensitizations, the reactions which occur generally are too irregular to be of any quantitative significance and are disregarded.

\*The dilutions are expressed as the proportion of serum to the dilution volume. Hence 1:1 indicates undiluted serum.

†The number of cutaneous reaction units (N) =  $(e-w)w/10$ , where  $e$  = the over-all diameter of the erythema and  $w$  the diameter of the wheal.

‡The expression, *in vitro* neutralization, is accepted nomenclature and here is not intended to imply that neutralization takes place prior to injection of the materials.

## STANDARDIZATION OF POLLEN EXTRACTS—WODEHOUSE

Twenty-four hours, or more, later the sites are retested for residual sensitization by injecting them with 0.01 c.c. of the standard pollen extract of five or more times the initial strength. As before, the lowest strength to give a reaction is regarded as the neutralizing point. The answer should be the same, or nearly so, by either method.

The *in vivo* method has the advantage of giving useful first-test reactions but a great disadvantage in requiring the accurate measurement of 0.01 c.c. in the critical test injections, an operation which has been found virtually impossible with the apparatus obtainable. The *in vitro* method has the disadvantage of almost completely sacrificing the first test reactions but the advantage of requiring the accurate injection of not less than 0.05 c.c. in the critical test. A high degree of accuracy is not necessary in the retest injections since the antigen is used in excess.

From either one of these trials, the range of serum dilutions requiring further investigation can be selected. The appropriate common ratio is calculated to construct a series of six dilutions within the limits chosen. Usually the common ratio will be less than 2x, which is closer than necessary for the purpose required. Serum dilutions are made in this series and tested by means of *in vitro* neutralization by equal volumes of the standard pollen extract of the same concentration as before. The reactions are measured and plotted in terms of their cutaneous reaction units. If the range has been properly chosen, the reaction curve will rise from approximately 0 and begin to level off before reaching the undiluted serum concentration. The levelling off region includes the optimal dilution of the serum for use against the standard pollen extract in concentrations at and below that used in the trial.

This serum-antigen ratio is a characteristic of the serum, relating it to the standard antigen and need only to be determined once. In actual practice the serum may be diluted more or less than this figure, but if this is done the concentration of standard antigen must be raised or lowered in the same proportion in order to be used with it. The only reason this ratio between the serum and extract cannot be used directly for measuring the serum-neutralizing capacity of the extract, thus using the serum as the standard, is that it varies with different skins and there are no standardized recipients. The problem must be approached indirectly.

*Standardizing the Working Extract.*—The appropriate dilution of the serum is made. The standard extract is diluted with normal saline solution without preservative in a series progressing by a common ratio, depending for its magnitude upon the range that the series is desired to cover and the number of sites to be used. The range is chosen to cover the probable difference between the standard and working extracts. If no information is available regarding the working extract, a preliminary trial is made to discover the approximate relation between it and the standard. For this purpose a series of dilutions of the standard with a common ra-

tio of from 3x to 5x is adjusted so the highest concentration is just strong enough to neutralize its site. Exactly the same dilutions are made of the extract to be standardized. Each antigen-dilution is combined with an equal volume of the diluted serum and, after thirty minutes at room temperature, they are used to prepare sites by injecting 0.05 c.c. endermally. The dilutions of the standard are placed at selected sites on one arm and those of the working extract at symmetrically opposite sides on the other arm of a normal recipient. The immediate reactions are recorded for what value they may have in detecting variations in skin sensitivity. Only rarely do they have real quantitative significance.

After twenty-four hours, or more, all sites are tested for neutralization with 0.01 c.c. of the standard antigen at a concentration in excess of the highest used in the first test. By comparing the reactions of the two series, those which correspond can be found with an error not greater than the common ratio of the series.

For the final trial, the standard is diluted to equal the approximate concentration of the working extract as found in the preliminary trial. Then from each is made a series of dilutions, using a small common ratio. That of 1.75x has been found to be the smallest to give reliable differentiation in a series of six tests.

Each dilution is mixed with an equal volume of diluted serum and used to prepare a series of sites which are retested twenty-four hours later, as before. Since this is the final trial, it is done in duplicate and it is necessary that the results of the two are the same. Otherwise they must be repeated.

Both the test and retest reactions are read and their cutaneous reaction values plotted. From the corresponding points on the two curves are found the relative strengths of the two within an error of not more than the common ratio of the dilution-series.

Standardization also may be done by *in vivo* neutralization. The *in vitro* method is preferred for the reasons already stated. Moreover, it requires one-third fewer injections. Similar results also may be obtained by serially diluting the serum and comparing on the dilutions the neutralizing effect of constant amounts of the standard and unknown antigens by either *in vitro* or *in vivo* neutralization.

#### APPLICATION OF THE METHOD

##### *Standardization of Sagebrush Pollen Extract*

*Determination of the Serum Concentration by In Vivo Neutralization.*—Serum KP was obtained from a hay-fever patient known to be clinically sensitive to sagebrush pollen and giving a 4 plus reaction to a 20,000-unit solution of it by scratch test. Six dilutions were made from this serum, progressing by a constant ratio of 3.5x. Six sites on the upper arm of a normal recipient were sensitized by endermal injection of 0.05 c.c. of each dilution.

## STANDARDIZATION OF POLLEN EXTRACTS—WODEHOUSE

Twenty-four hours later each site was tested with 0.01 c.c. standard sagebrush, 100 units per cubic centimeter. All sites reacted (Table I). That of dilution 1:525 had a value of only 2.1 cutaneous reaction units.

TABLE I. FINDING APPROPRIATE  
SERUM DILUTION BY IN VIVO  
NEUTRALIZATION

271		Serum K.P. Recipient R. P. W.					
Site Nos.	Serum Dilus. Ratio 3.5 x	Test: Sagebrush Stand. 100 u.p.c.c.			Retest: Sagebrush Stand. 500 u.p.c.c.		
		W	E	Cru.	W	E	Cru.
1	1:525	7	10	2.1	7	0	0
2	1:150	9	20	9.9	7	0	0
3	1:43	9	25	14.4	7	0	0
4	1:12.25	13	25	15.6	6	8	1.2
5	1:3.5	12	25	15.6	11	20	9.9
6	1:1	12	25	15.6	12	20	9.6

Reactions of sites sensitized with 0.05 c.c. KP serum dilutions, tested twenty-four hours later with 0.01 c.c. standard sagebrush No. 64, 100 units per cubic centimeter, and retested three days later with 0.01 c.c. standard sagebrush, 500 units per cubic centimeter. (See Fig. 1).

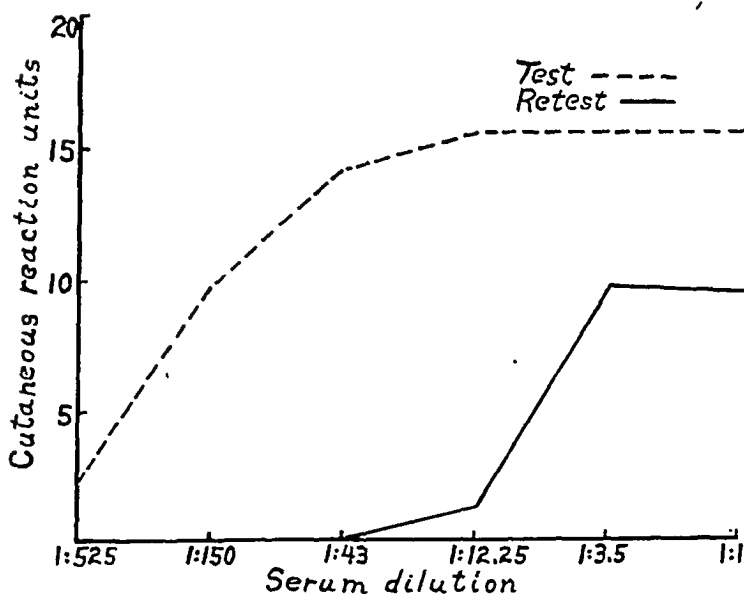


Fig. 1. Reactions of sites of varying sensitization tested and retested with sagebrush pollen extract, as in Table I.

From this the reactions rose to 15.6 reaction units at a dilution of 1:12.25, but beyond this there was no further increase in reaction size with increasing serum concentration (Fig. 1). This is the ceiling or levelling off of the reaction-curve obtainable with 0.01 c.c. of 100-unit sagebrush. To secure larger reactions with the higher concentrations of serum, it would be necessary to use a higher concentration of the antigen.

# STANDARDIZATION OF POLLEN EXTRACTS—WODEHOUSE

To discover the degree of neutralization by these reactions, the sites were retested three days later with 0.01 c.c. standard sagebrush, 500 units per cubic centimeter. The sites sensitized with the three lower concen-

TABLE II. FINDING APPROPRIATE  
SERUM DILUTION BY IN VITRO  
NEUTRALIZATION

272A		Serum K.P. Recipient P.B.					
Site Nos.	Serum Dilus. Ratio 3.5 x	Test: Serum Dilus. + Sagebrush			Retest: Sagebrush 500 Units per c.c.		
		W	E	Cru.	W	E	Cru.
1	1:525	12	0	0	5	0	0
2	1:150	10	0	0	5	0	0
3	1:43	13	40	35.1	6	8	1.2
4	1:12.25	14	20	8.4	5	7	1.0
5	1:3.5	12	20	9.6	9	35	23.4
6	1:1	11	20	9.9	9	35	23.4

Reactions of normal sites tested with 0.10 c.c. of dilutions of KP serum in a series progressing by 3.5x, + standard sagebrush, No. 64, 100 units per cubic centimeter, combined in equal parts; and to their retests with 0.01 c.c. standard sagebrush, 500 units per cubic centimeter. (See Fig. 2).

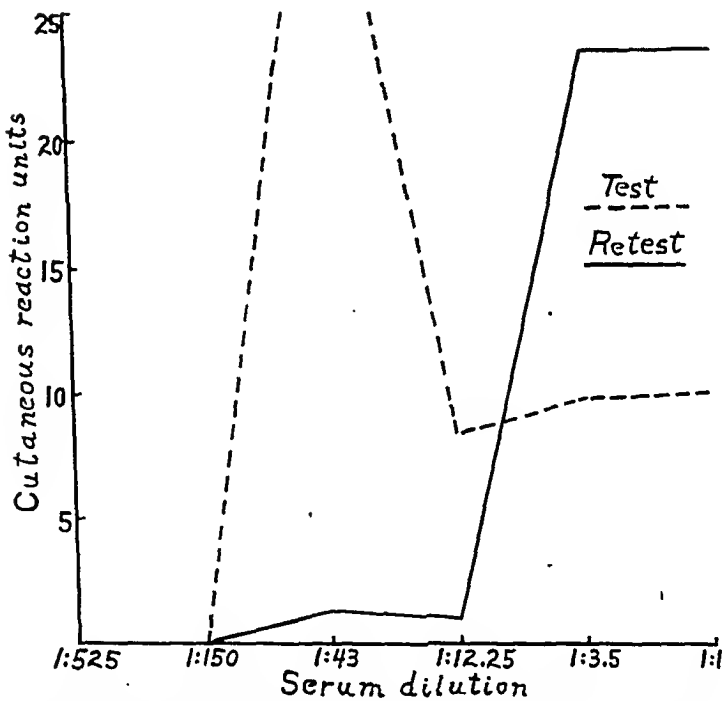


Fig. 2. Reactions of normal sites to combinations of sagebrush pollen extract with varying amounts of homologous serum, and their retests with sagebrush, as in Table II.

trations of serum showed complete neutralization by the previous injection of sagebrush pollen extract. The site of serum dilution 1:12.25 gave only a borderline reaction of 1.2 cutaneous reaction units. This was the point at



# STANDARDIZATION OF POLLEN EXTRACTS—WODEHOUSE

which the test curve began to level off (Fig. 1). From this point the reaction size jumped to 9.9 at the site of serum dilution of 1:3.5, but showed no further increase with increasing serum concentration, probably be-

TABLE III. FINDING APPROPRIATE  
SERUM DILUTION BY IN VITRO  
NEUTRALIZATION

272B		Serum K.P. Recipient P.B.					
Site Nos.	Serum Dilus. Ratio 1.4 x	Test: Serum Dilus. + Sagebrush			Retest: Sagebrush 500 units per c.e.		
		W	E	Cru.	W	E	Cru.
1	1:21.5	13	0	0	5	0	0
2	1:15.3	9	0	0	5	7	1
3	1:11	13	0	0	5	12	3.5
4	1:7.8	12	13	1.2	7	35	19.6
5	1:5.6	12	22	12.1	7	30	16.1
6	1:4	11	30	20.9	7	30	16.1

Reactions of normal sites tested with 0.10 c.c. of dilutions of KP serum in a series progressing by 1.4x + standard sagebrush, No. 64, 100 units per cubic centimeter, combined in equal parts; and to their retests with 0.01 c.c. standard sagebrush, 500 units per cubic centimeter. (See Fig. 3).

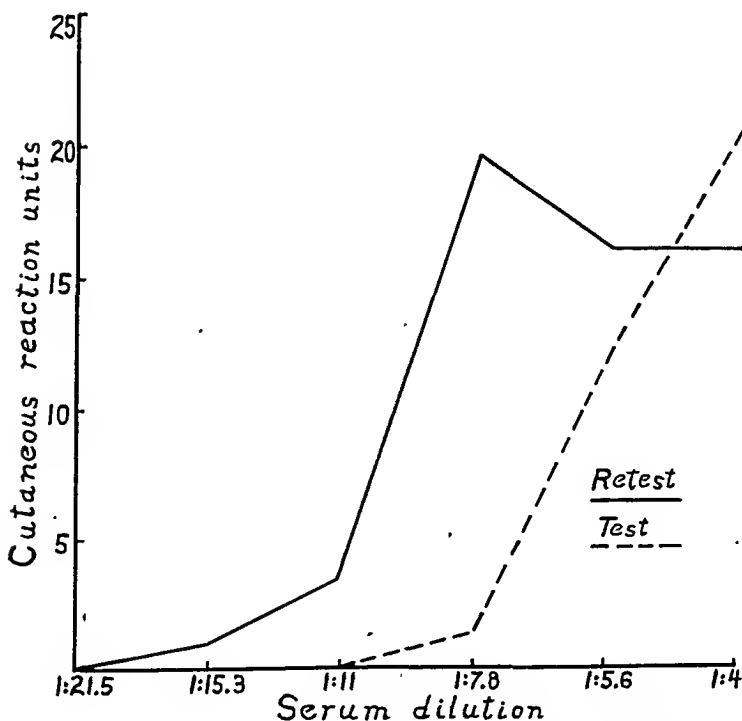


Fig. 3. Reactions of normal sites to combinations of sagebrush pollen extract with varying amounts of homologous serum, and their retests with sagebrush, as in Table III.

cause this is the ceiling for 0.01 c.c. of 500-unit sagebrush. It shows that for use with this concentration of sagebrush the serum concentration must be above 1:12.25 but need not be above 1:3.5.

## STANDARDIZATION OF POLLEN EXTRACTS—WODEHOUSE

TABLE IV. STANDARDIZATION OF SAGEBRUSH EXTRACT

277	Standard Sagebrush, No. 64						R.	L.	X Sagebrush						X Pollen Units Per c.e.
Stand. Pollen Units Per c.c.	Test: Serum + Pollen Dilus.			Retest: Sagebrush Stand. 300 u.p.e.e.			Site Nos.	Test: Serum + Pollen Dilus.			Retest: Sagebrush Stand. 300 u.p.e.e.				
	W	E	Cru.	W	E	Cru.		W	E	Cru.	W	E	Cru.		
0	8	0	0	9	50	36.9	6	10	0	0	10	10	30	0	
0.32	8	20	9.6	9	50	36.9	1	8	0	0	10	60	50	1.6	
1.6	7	12	3.5	9	50	36.9	2	10	0	0	9	50	30.9	8	
8	9	20	9.9	8	45	29.6	3	10	12	2	9	45	32.4	40	
40	7	30	16.1	8	50	33.6	4	10	20	10	9	40	27.9	200	
200	8	20	9.6	6	10	2.4	5	9	15	5.4	9	35	23.4	1000	

Reactions of normal sites tested with serial dilutions of standard sagebrush + KP serum compared with those to X sagebrush + KP serum; and as retested with standard sagebrush.

First test: 0.05 c.c. KP serum, 1:8, + equal volumes of dilutions of sagebrush, on the right arm standard and on the left X, progressing by a common ratio of 5.

Retest: Twenty-four hours later all sites tested with 0.01 c.c. standard sagebrush, 300 units per cubic centimeter.

#### Determination of Serum Concentration by In Vitro Neutralization.—

Dilutions of the serum were made as before. Before being injected, each was combined with an equal volume of standard sagebrush, 100 units per cubic centimeter. After one-half hour *in vitro* at room temperature, 0.1 c.c. of the combinations were injected into each of six sites (Table II). The immediate reactions were meaningless beyond suggesting that site No. 3 was more sensitive than the others.

Twenty-four hours later all sites were tested for residual sensitization with 0.01 c.c. standard sagebrush 500 units per cubic centimeter (Table II). The sites of the two lowest serum concentrations were found to be completely neutralized. The 1:43 site showed only a negligible activity and this probably was because this site was extraordinarily sensitive, as indicated by the first test. From the 1:12.25 dilution showing only a trace of reaction, the reaction jumped to 23.4 reaction units but showed no further increase, which essentially was the story told in the previous trial by *in vivo* neutralization. The trial showed, as before, that for neutralization tests with standard sagebrush extracts up to and including 100 units per cubic centimeter, the optimal dilution of KP serum will be found between 1:12.25 and 1:3.5.

To find the optimal dilution more exactly, dilutions of the serum were made, progressing by a constant ratio of 1.4x covering this range and extending somewhat beyond at both ends. The trial was made as before *in vitro* (Table III, Fig. 3). The result showed that the optimal concentration for this serum is about 1:7.8. A dilution of 1:8 was chosen for use with concentrations of standard sagebrush ranging from about 100 units per cubic centimeter downwards.

Testing the Working Extract.—Sagebrush X was submitted for standardization. It was known only to be weaker but believed to be much weaker than standard which was 20,000 standard nitrogen units per cubic

## STANDARDIZATION OF POLLEN EXTRACTS—WODEHOUSE

TABLE V. STANDARDIZATION OF SAGEBRUSH EXTRACT

279	Standard Sagebrush No. 64						R.	L.	X Sagebrush					
Stand. Pollen Units Per c.e.	Test: Serum + Stand. Pollen Dilus.			Retest: Sagebrush Stand. 500 u.p.e.e.			Site Nos.	Test: Serum + X Pollen Dilus.			Retest: Sagebrush Stand. 500 u.p.e.e.			X Pollen Units Per c.e.
	W	E	Cru.	W	E	Cru.		W	E	Cru.	W	E	Cru.	
0	9	0	0	11	40	31.9	6	10	16	6	11	40	31.9	0
28.82	8	12	3.2	8	40	25.6	1	9	0	0	9	45	32.4	720.5
50.42	9	18	8.1	9	35	23.4	2	9	15	5.4	9	35	23.4	1260
88.23	9	12	2.7	9	30	18.9	3	9	0	0	9	40	27.9	2206
154.4	10	17	7.0	6	15	5.4	4	9	15	5.4	10	40	30.	3860
270.2	10	15	5.0	5	8	1.5	5	9	20	9.9	9	40	27.9	6755

Reactions of normal sites tested with serial dilutions of standard sagebrush + KP serum, compared with those to X sagebrush + KP serum; and as retested with standard sagebrush.

First test: 0.05 c.c. KP serum, 1:8 + equal volumes of dilutions of sagebrush, on the right arm standard and on the left, corresponding dilutions of X sagebrush, at twenty-five times the standard both progressing by a common ratio of 1.75x. (See Fig. 4).

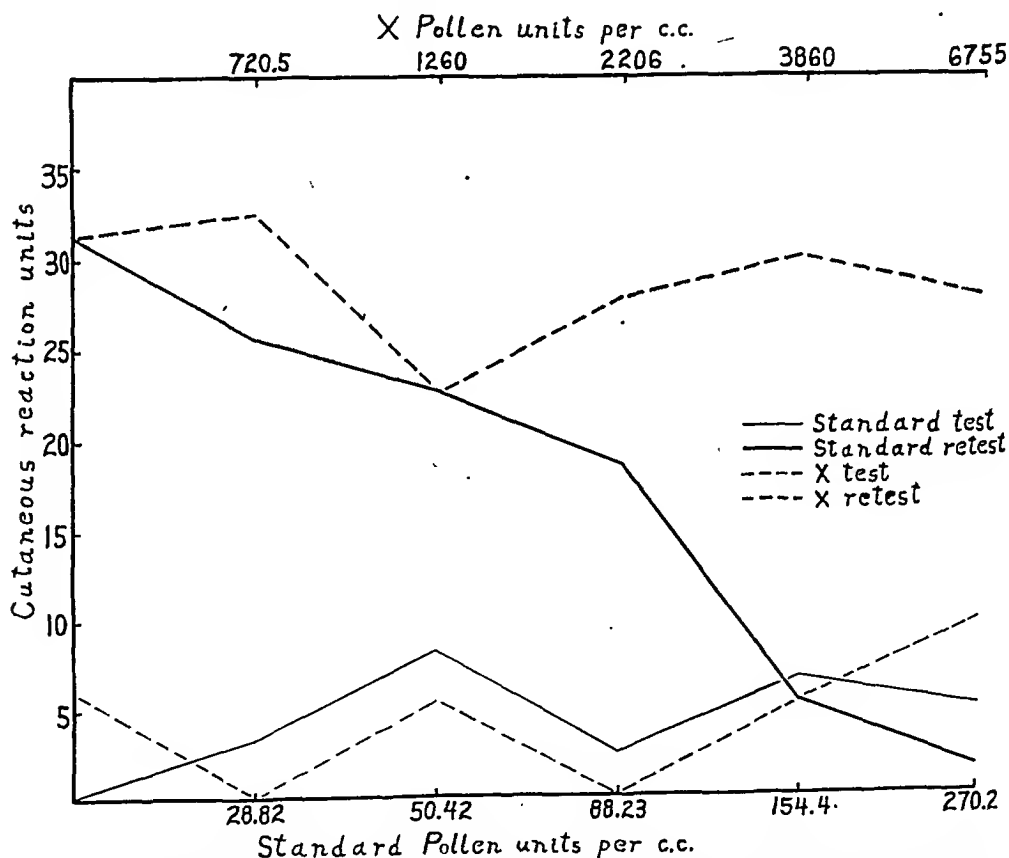


Fig. 4. Reactions of normal sites to combinations of sensitizing serum with standard sagebrush compared with similar combinations with X sagebrush, and to their retests with standard sagebrush, as in Table V.

centimeter. The standard was diluted to 200 standard nitrogen units per cubic centimeter and a series of dilutions, progressing by the common ratio of 5x, made from it. To X was assigned a provisional value of 20,000 X units per cubic centimeter. It was diluted in exactly the same way as the standard. The two series were compared by *in vitro* neutralization on

# STANDARDIZATION OF POLLEN EXTRACTS—WODEHOUSE

TABLE VI. STANDARDIZATION OF SAGEBRUSH EXTRACT

280	Standard Sagebrush						R.	L.	X Sagebrush					
Stand. Pollen Units Per c.c.	Test: Serum + Stand. Pollen Dilus.			Retest: Sagebrush Stand. 500 u.p.c.c.			Site Nos.	Test: Serum + X Pollen Dilus.			Retest: Sagebrush Stand. 500 u.p.c.c.			X Pollen Units Per c.c.
	W	E	Cru.	W	E	Cru.		W	E	Cru.	W	E	Cru.	
0	7	25	12.6	12	40	33.6	6	8	15	5.6	11	40	31.9	0
28.82	7	25	12.6	8	45	29.6	1	7	25	12.6	8	50	33.6	720.5
50.42	8	30	17.6	8	35	21.6	2	8	30	17.6	8	45	29.6	1260
88.23	7	15	5.6	7	30	16.1	3	9	25	14.4	9	40	27.9	2206
154.40	8	20	9.6	5	9	2.0	4	8	15	5.6	8	35	21.6	3860
270.20	7	18	7.7	5	0	0	5	9	20	9.9	9	40	27.9	6755

All tests as in previous trial, Table V. (See Fig. 5).

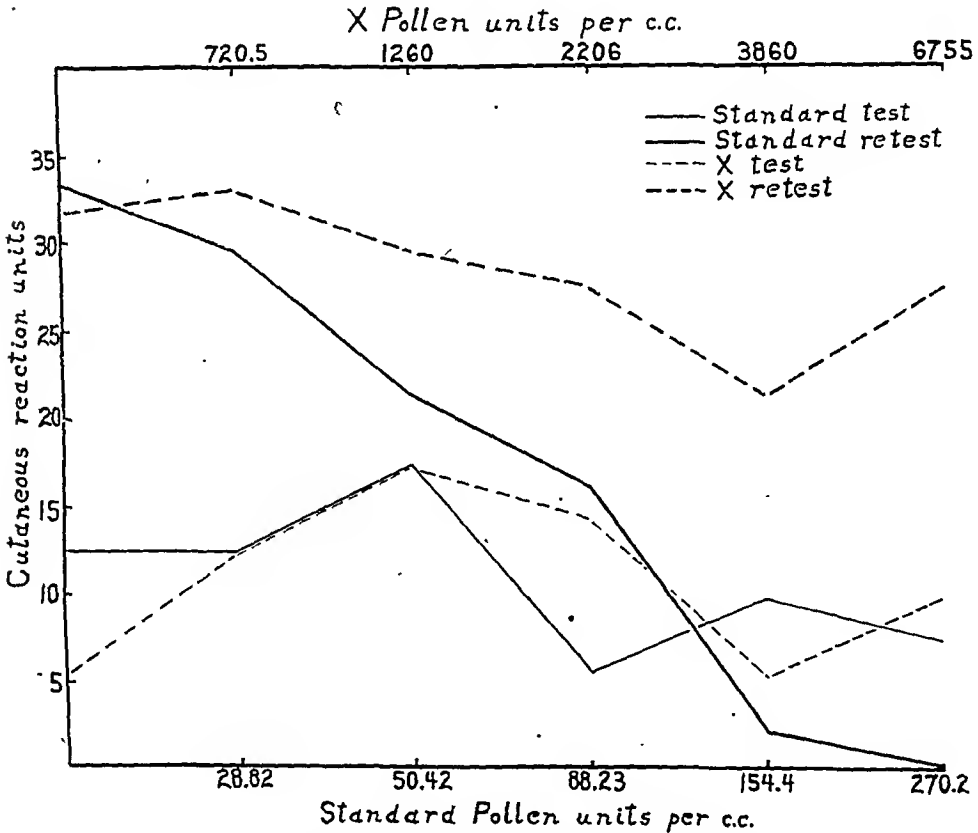


Fig. 5. Reactions of normal sites to combinations of sensitizing serum with standard sagebrush compared with similar combinations with X sagebrush, and to their retests with standard sagebrush, as in Table VI.

opposite arms of the same recipient (Table IV). Retested with 0.01 c.c. of 300-unit sagebrush, the standard showed no neutralization to 40 units. From that point to 200 units almost complete neutralization took place. X was probably starting a similar drop at its full concentration (1000 X units). If so, X was  $1/5 \times 1/5 = 1/25$  as strong as the standard. This was put to the test in the next trials (Tables V and VI). In these the standard was diluted in a series progressing by the common ratio of 1.75x

## STANDARDIZATION OF POLLEN EXTRACTS—WODEHOUSE

TABLE VII. STANDARDIZATION OF SAGEBRUSH EXTRACT

281	Standard Sagebrush						R.	L.	X Sagebrush					
Stand. Pollen Units Per c.c.	Test: Serum + Stand. Pollen Dilus.			Retest: Sagebrush Stand. 500 u.p.c.c.			Site Nos.	Test: Serum + X Pollen Dilus.			Retest: Sagebrush Stand. 500 u.p.c.c.			X Pollen Units Per c.c.
	W	E	Cru.	W	E	Cru.		W	E	Cru.	W	E	Cru.	
0	14	0	0	13	35	28.6	6	7	0	0	13	35	28.6	0
14.41	10	0	0	7	25	12.6	1	5	0	0	7	30	16.1	1441
25.21	10	15	5	7	20	9.1	2	7	0	0	7	30	16.1	2521
44.12	10	0	0	7	20	9.1	3	8	0	0	7	20	9.1	4412
77.2	10	0	0	7	10	2.1	4	10	14	4.0	8	10	1.6	7720
135.1	14	0	0	6	14	4.8	5	12	15	3.6	6	12	3.6	13510

As in Table V, except that the serum concentration is 1:16, one half that used in the preceding trial, and the standard dilutions are also one-half those of the preceding trial but the X dilutions are doubled. These adjustments were made according to the indications of the preceding trial. (See Fig. 6.)

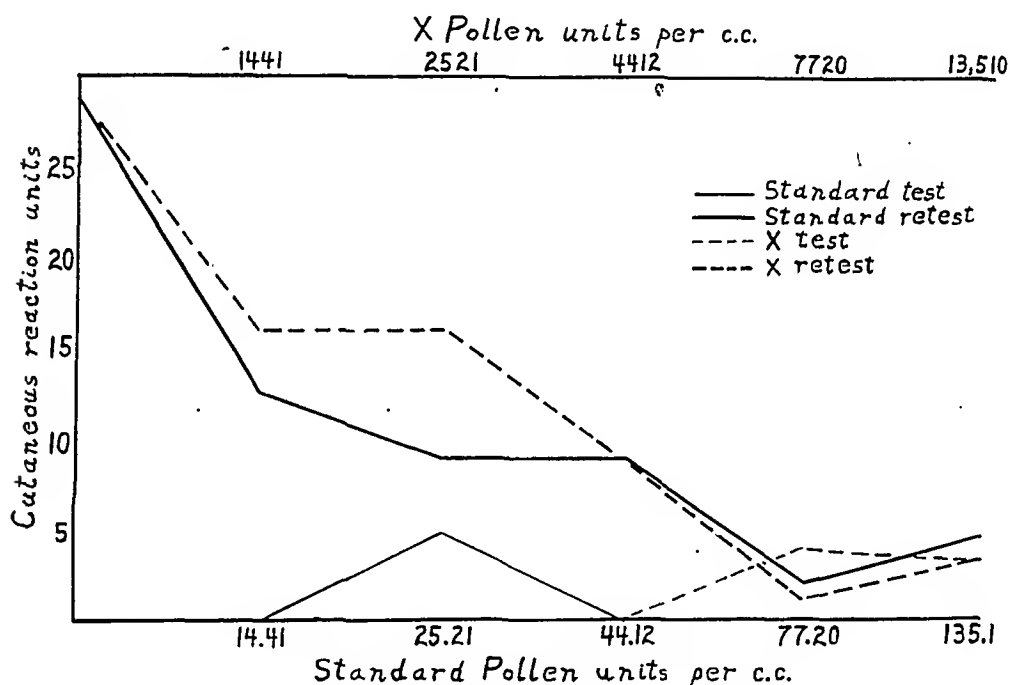


Fig. 6. As in Figure 5 except that the serum and standard sagebrush dilutions are used at half strength while those of X sagebrush are used at double strength. See Table VII.

with maximum concentration at 270.2 units per cubic centimeter. It was estimated that the latter would just neutralize the serum. X was diluted in a similar series, but twenty-five times as concentrated in X units as the standard. In the first trial (Table V), the retests showed that concentrations 6,755 and 3,860 X units almost corresponded to 50.42 and 28.82 standard units, respectively, about three steps apart in the series, but in the second trial (Table VI) 3,860 and 2,206 X units almost corresponded to 50.42 and 28.82 standard units, or about two steps apart in the series. The correct estimate therefore would be between two and three steps in the series. Accordingly, a ratio between the two series of 4 was chosen for the next trial.

It was impossible to increase the X concentration four times because

## STANDARDIZATION OF POLLEN EXTRACTS—WODEHOUSE

TABLE VIII. STANDARDIZATION OF RAGWEED EXTRACT

267	Standard Ragweed						R.	L.	X Ragweed					
Stand. Pollen Units Per c.c.	Test: Serum + Stand. Pollen Dilus.			Retest: Stand. Ragw'd 1000 u.p.c.c.			Site Nos.	Test: Serum + X Pollen Dilus.			Retest: Stand. Ragw'd 1000 u.p.c.c.			X Pollen Units Per c.c.
	W	E	Cru.	W	E	Cru.		W	E	Cru.	W	E	Cru.	
0	0	0	0	10	50	40	6	0	0	0	10	50	40	0
2	8	30	17.6	8	20	9.6	5	0	0	0	10	45	35	2
10	9	35	23.4	5	7	1	4	10	12	2	9	40	27.9	10
50	10	35	25.0	0	0	0	3	8	20	9.6	9	40	27.9	50
250	9	40	27.9	0	0	0	2	10	30	20	6	14	4.8	250
1250	10	22	12.0	0	0	0	1	10	45	35	2	5	0.6	1250

Reactions of normal sites to standard ragweed dilutions + equal volumes of ragweed-sensitive serum, and their reactions when retested with ragweed alone; compared with X ragweed dilutions treated in the same way. (See Fig. 7).

First tests: 0.05 c.c. of SK serum, 1:5, + serial dilutions, progressing by 5x, of standard ragweed symmetrically opposite corresponding dilution of X ragweed.

Second tests: 0.01 c.c. twenty-four hours later, standard ragweed, 1000 units per cubic centimeter.

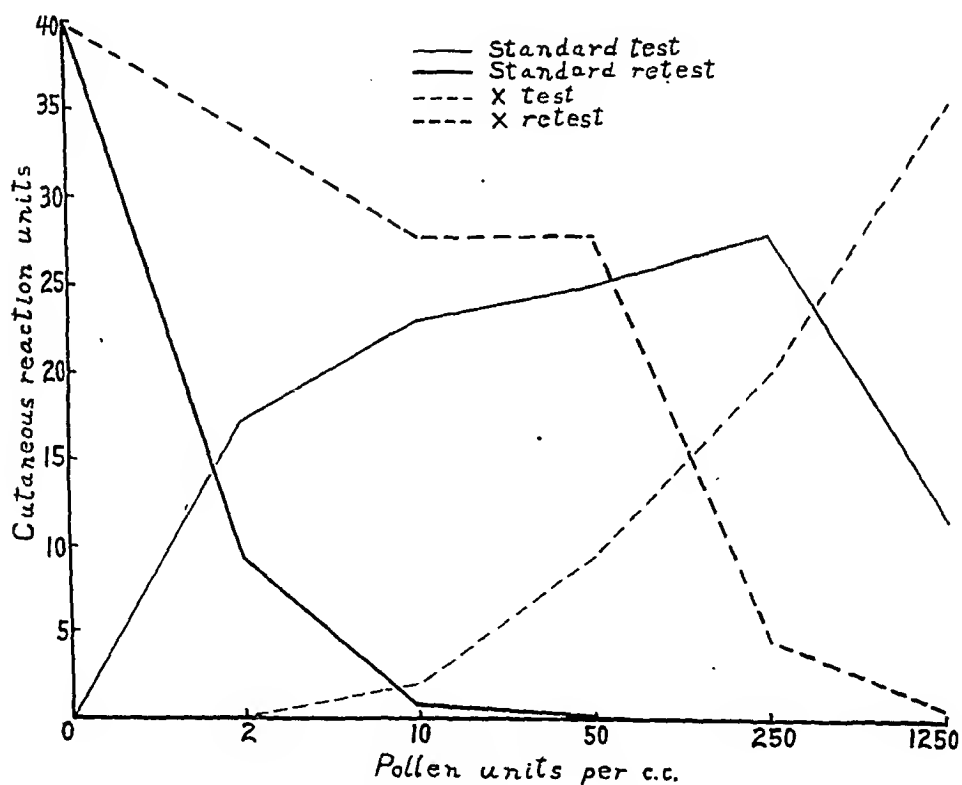


Fig. 7. Reactions of normal sites to combinations of sensitizing serum with standard ragweed compared with X ragweed, and their retests, as shown in Table VIII.

undiluted it was only 20,000 X units. Consequently, X was doubled and the standard was halved. At the same time the serum concentration was halved to 1:16, to maintain the relation between it and the standard which had proved in the two trials to be quite properly adjusted. When these two series of dilutions were tested it was found that X neutralized about the

# STANDARDIZATION OF POLLEN EXTRACTS—WODEHOUSE

TABLE IX. STANDARDIZATION OF RAGWEED EXTRACT

269	Standard Ragweed						R.	L.	X Ragweed					
Stand. Pollen Units Per c.c.	Test: Serum + Stand. R'gw'd Dilus.			Retest: Stand. Ragw'd 1000 u.p.c.e.			Site Nos.	Test: Serum + X Ragweed Dilus.			Retest: Stand. Ragw'd 1000 u.p.c.e.			X Pollen Units Per c.c.
	W	E	Cru.	W	E	Cru.		W	E	Cru.	W	E	Cru.	
0	6	0	0	12	45	39.6	6	6	0	0	12	50	45.6	0
1.54	8	20	9.6	10	50	40.0	5	6	15	5.4	9	50	36.9	61.6
2.70	7	25	12.6	7	35	19.6	4	8	25	13.6	7	35	19.6	108.1
4.72	8	20	9.6	7	35	19.6	3	6	20	8.4	7	40	23.1	188.8
8.27	7	20	9.1	8	10	1.6	2	8	30	17.6	6	15	5.4	330.8
14.48	7	20	9.1	5	0	0	1	8	30	17.6	5	0	0	579.2

Reactions of normal sites to standard ragweed dilutions + equal volumes of ragweed-sensitive serum, and their reactions when retested with ragweed alone; compared with X ragweed dilutions treated in the same way.

First tests: 0.05 c.c. of SK serum 1:5 + equal parts of serial dilutions, progressing by 1.75x, of standard ragweed symmetrically opposite corresponding dilutions of X ragweed, at 40x standard.

Retests: 0.01 c.c., 24 hours later, ragweed standard, 1000 units per cubic centimeter. (See Fig. 8.)

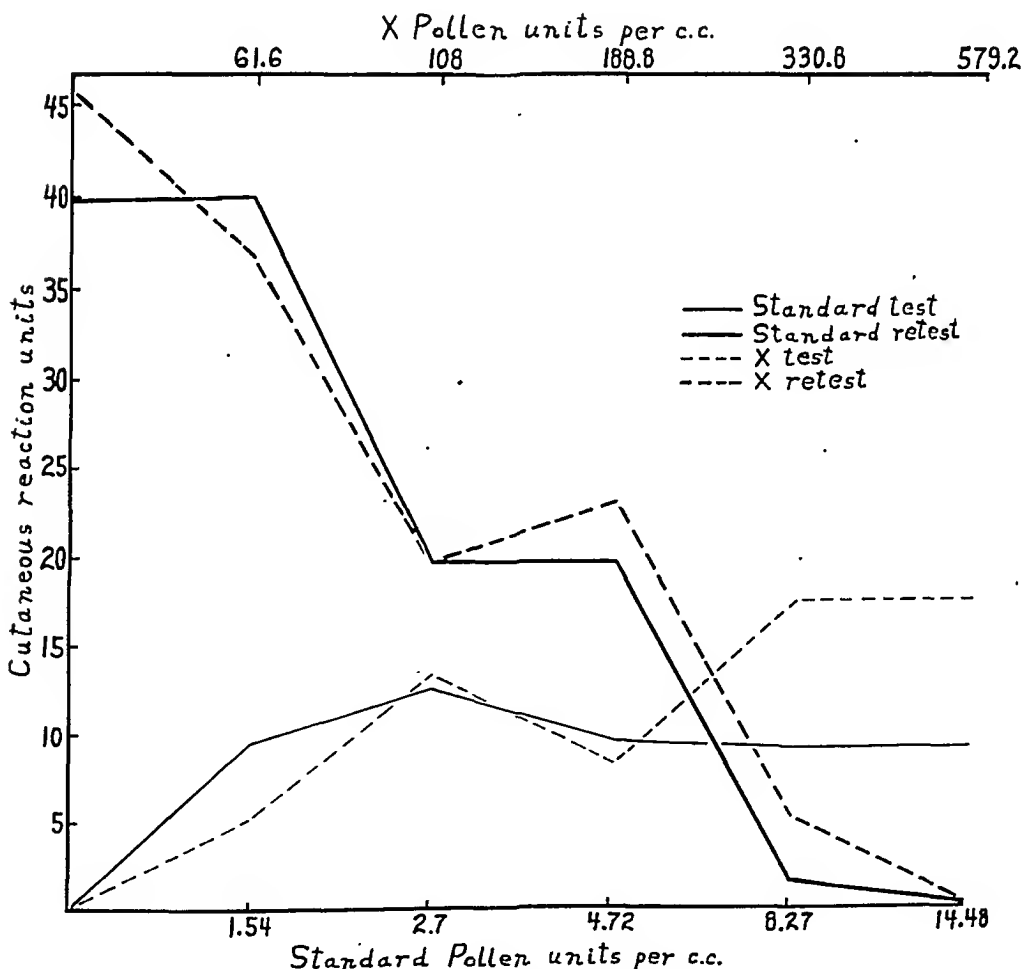


Fig. 8. As in Figure 7, except that the dilutions are in series progressing by the common ratio of 1.75 and those of X 40-times as concentrated as previously, as in Table IX.

## STANDARDIZATION OF POLLEN EXTRACTS—WODEHOUSE

TABLE X. STANDARDIZATION OF RAGWEED EXTRACT

270	Standard Ragweed						R.	L.	X Ragweed					
Stand. Pollen Units Per c.c.	Test: Serum + Stand. R'gw'd Dilus.			Retest: Stand. Ragw'd 1000 u.p.c.c.			Site Nos.	Test: Serum + X Ragweed Dilus.			Retest: Stand. Ragw'd 1000 u.p.c.c.			X Pollen Units Per c.c.
	W	E	Cru.	W	E	Cru.		W	E	Cru.	W	E	Cru.	
0	7	0	0	10	50	40	6	7	0	0	10	50	40	0
1.54	8	40	25.6	9	45	32.4	5	8	30	17.6	9	50	36.9	61.6
2.70	11	40	31.9	8	35	21.6	4	10	50	40.0	9	35	23.4	108.0
4.72	7	45	26.6	9	40	27.9	3	7	45	26.6	8	25	13.6	188.8
8.27	9	45	32.4	7	30	16.1	2	9	45	32.4	9	25	14.4	330.8
14.48	10	45	45.0	4	15	4.4	1	10	55	45.0	4	10	2.4	579.2

Tests all the same as in Table IX. (See Fig. 9).

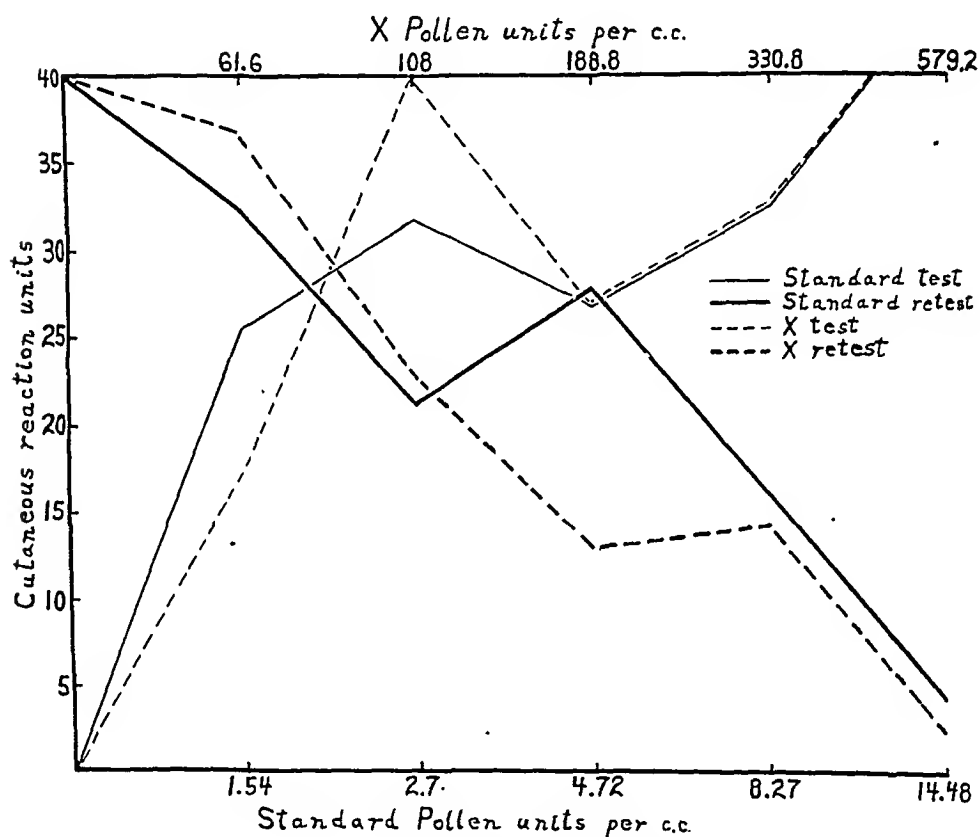


Fig. 9. As in Figure 8. See Table X.

same amount of reagin as the standard (Table VII, Fig. 6). Therefore, in this adjustment which balanced 100 X units against one of standard, the two extracts were of equal potency. It was concluded that X was 1/100 the strength of standard. This was found to be correct. X had been prepared, unknown to the investigators, by diluting the standard 1:10 and again 1:10 by two different investigators not in collaboration.



## STANDARDIZATION OF POLLEN EXTRACTS—WODEHOUSE

### STANDARDIZATION OF RAGWEED POLLEN EXTRACT

An extract of combined ragweed pollen (tall and short, equal parts) was submitted for standardization. It was known only to be weaker than the standard.

Ragweed-sensitive serum SK was chosen to be used, on the basis of previous experiments, at a dilution of 1:5.

The ragweed standard of 20,000 units per cubic centimeter was diluted in a series progressing by a common ratio of 5x. Ragweed X was assigned a provisional value of 20,000 X units per cubic centimeter, and diluted in the same way as the standard. Both series of dilutions were combined with equal volumes of the diluted serum and the combinations used to prepare sites as before, placing corresponding dilutions of each series symmetrically opposite each other (Table VIII). The immediate reactions suggested that the standard was very much stronger than X. Twenty-four hours later all sites were retested with 0.01 c.c. of standard ragweed, 1,000 units per cubic centimeter, to discover the extent of neutralization. The curve (Fig. 7) showed that X was less than  $1/25$  but more than  $1/250$  of the standard; in other words, X was between 800 and 80 standard units of potency and obviously much closer to the former. So, for the next trial X was assumed to be 500 standard units of potency, or  $1/40$  the strength of the standard.

The standard extract was diluted to 14.48 units per cubic centimeter, which, it was estimated, would just neutralize the sites, and from this was made a series of dilutions progressing by a common ratio of 1.75x. Pollen extract X was diluted to 579.2 X units, that is, 40 times the concentration of standard in terms of X units, and this was diluted in series in the same way as the standard. These series were compared twice, using two recipients (Tables IX and X). In the retests of both trials, the two extracts were found to have neutralized their corresponding sites to approximately the same extent. And when the reactions were plotted coordinately (Figs. 8 and 9) neither curve was consistently above the other; hence the two extracts, as adjusted, were equal, i.e., X was  $1/40$  the potency of the standard.

Then it was revealed to the investigators that the X extract had been prepared from the standard by diluting it to 500 units or to  $1/40$  of the standard.

### PREPARATION OF A NEW STANDARD

In the ordinary course of events standards must be renewed. The following experiment was done to simulate the procedure for replacing or replenishing the standard by the addition of new pollen, although in this instance standard procedures were not observed in the preparation of the extracts as they would be in actual practice. Two timothy extracts (No. 40 and No. 65) were chosen for comparison. They had been made for experimental purposes at different times, from different batches of pollen,

STANDARDIZATION OF POLLEN EXTRACTS—WODEHOUSE

TABLE XI. ESTABLISHING A NEW TIMOTHY STANDARD

274	Timothy Standard No. 40						R.	L.	Timothy No. 65					
Pollen No. 40 Units Per c.c.	Test: Serum + Timothy 40 Dilus.			Retest: Timothy No. 40, 100 u.p.c.c.			Site Nos.	Test: Serum + Timothy 65 Dilus.			Retest: Timothy No. 40, 100 u.p.c.c.			Pollen No. 65 Units Per c.c.
	W	E	Cru.	W	E	Cru.		W	E	Cru.	W	E	Cru.	
0	5	0	0	11	55	48.4	6	0	0	0	11	60	53.9	0
1.87	10	50	40	6	40	20.4	1	10	50	40	6	30	14.4	1.87
3.28	8	30	17.6	7	20	9.1	2	10	50	40	7	20	9.1	3.28
5.73	10	50	40	7	35	19.6	3	9	50	36.9	6	12	3.6	5.73
10.03	9	40	27.9	5	0	0	4	10	50	40	5	0	0	10.03
17.56	9	50	36.9	6	0	0	5	9	40	27.9	5	0	0	17.56

Reactions of normal sites to timothy No. 40 dilutions + equal volumes of timothy-sensitive serum, and their reactions when retested with timothy alone; compared with reactions from timothy 65 dilutions treated in the same way. (See Fig. 10).

First tests: 0.05 c.c. JB serum + serial dilutions of timothy No. 40, progressing by 1.75x symmetrical opposite corresponding dilutions of timothy 65.

Second tests: 0.01 c.c., twenty-four hours later, timothy 40, 1000 units per cubic centimeter.

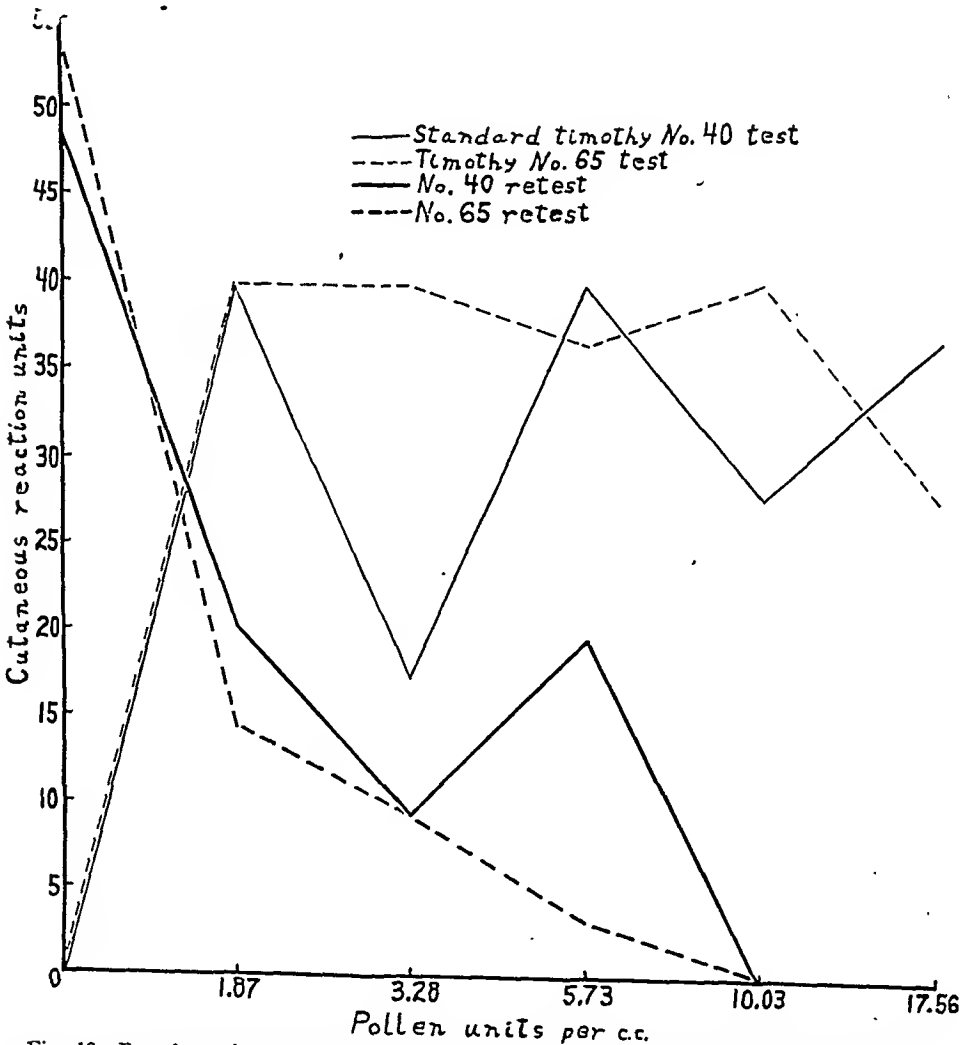


Fig. 10. Reactions of normal sites to timothy standard No. 40 dilutions + equal volumes of homologous serum, and their reactions when retested with timothy alone; compared with reactions of timothy No. 65 dilutions treated in the same way, as in Table XI.

## STANDARDIZATION OF POLLEN EXTRACTS—WODEHOUSE

TABLE XII. ESTABLISHING A NEW TIMOTHY STANDARD

275	Timothy Standard No. 40						R.	L.	Timothy No. 65					
Pollen No. 40 Units Per c.c.	Test: Serum + Timothy 40 Dilus.			Retest: Timothy No. 40, 100 u.p.c.c.			Site Nos.	Test: Serum + Timothy 60 Dilus.			Retest: Timothy No. 40, 100 u.p.c.c.			Pollen No. 65 Units Per c.c
	W	E	Cru.	W	E	Cru.		W	E	Cru.	W	E	Cru.	
0	0	0	0	10	50	40	6	0	0	0	11	40	31.9	0
0.88	8	20	9.6	7	45	26.6	1	8	30	17.6	7	35	19.6	0.88
1.54	9	20	9.9	8	30	17.6	2	9	35	23.4	7	22	10.5	1.54
2.70	8	35	21.6	7	40	23.1	3	9	35	23.4	7	30	16.1	2.70
4.73	8	30	17.6	7	25	12.6	4	9	40	27.9	6	22	9.6	4.73
8.27	9	40	27.9	6	35	17.4	5	9	40	27.9	5	15	5.0	8.27

Tests the same as Table XI, except that the two pollen series were adjusted to a lower level to get less neutralization of the sites. (See Fig. 11).

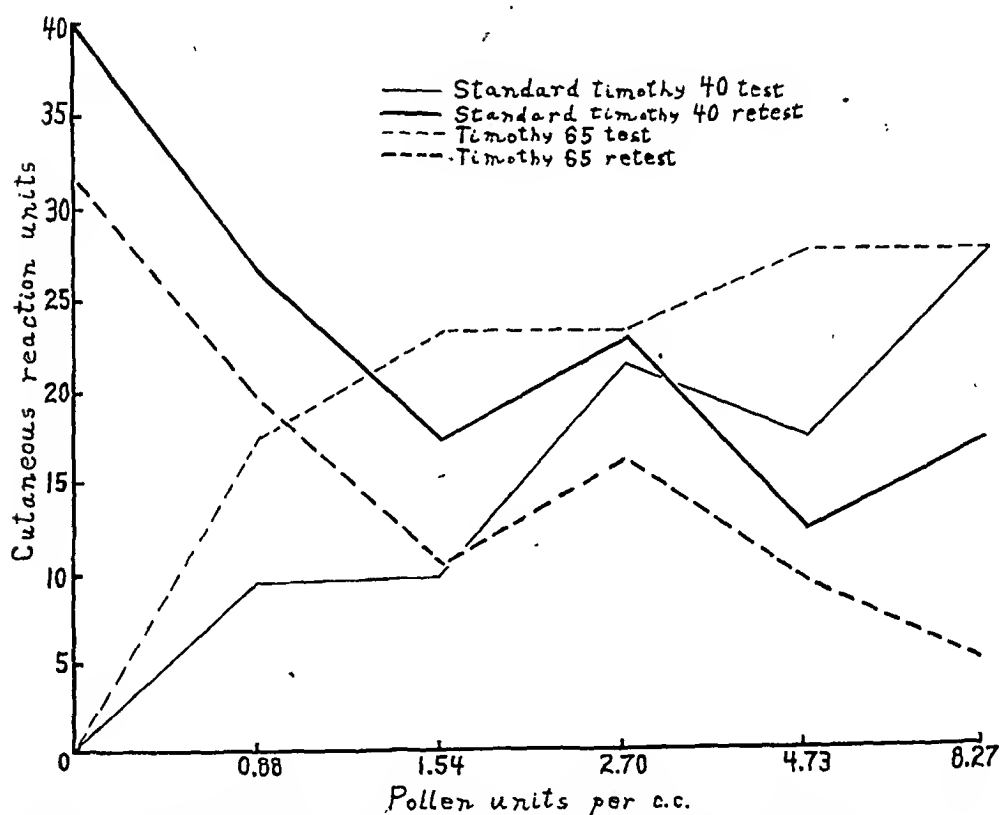


Fig. 11. As in Figure 10, except that the two series of dilutions are adjusted to a lower level to get less neutralization. See Table XII.

and by different techniques. They had in common 20,000 nitrogen units per cubic centimeter and were preserved with 50 per cent glycerine.

Since it was not known if one was stronger than the other, it was assumed that they were of nearly the same potency, and the preliminary trial was made with serial dilutions progressing by the small common ratio of 1.75x. The two series were compared in their neutralizing capacity for a timothy-sensitive serum by *in vitro* neutralization (Table XI, Fig. 10). The first test reaction showed extraordinary irregularities in the right

TABLE XIII. ESTABLISHING A NEW TIMOTHY STANDARD

276	Timothy No. 40						R.	L.	Timothy No. 65					
Pollen No. 40 Units Per c.e.	Test: Serum + Timothy 40 Dilus.			Retest: Timothy No. 40, 100 u.p.c.e.			Site Nos.	Test: Serum + Timothy 65 Dilus.			Retest: Timothy No. 40, 100 u.p.c.e.			Pollen No. 65 Units Per c.e.
	W	E	Cru.	W	E	Cru.		W	E	Cru.	W	E	Cru.	
0	9	0	0	10	40	30.0	6	11	0	0	10	40	30	0
0.88	8	25	13.6	6	35	17.4	1	10	40	30	7	30	16.1	0.44
1.54	9	30	18.9	6	30	14.4	2	8	35	21.6	6	30	14.4	0.77
2.70	10	35	25.0	4	12	3.2	3	11	40	31.9	4	12	3.2	1.35
4.73	8	30	17.6	7	25	12.6	4	8	30	17.6	6	25	11.4	2.36
8.27	10	40	30.0	5	11	3.0	5	10	40	30	5	12	3.5	4.13

Tests the same as in Table XII, except that the dilutions of timothy 65 are just one-half those of timothy 40. The trial shows that so adjusted the two extracts are of equal potency; therefore, timothy 65 is double the potency of timothy 40. (See Fig. 12).

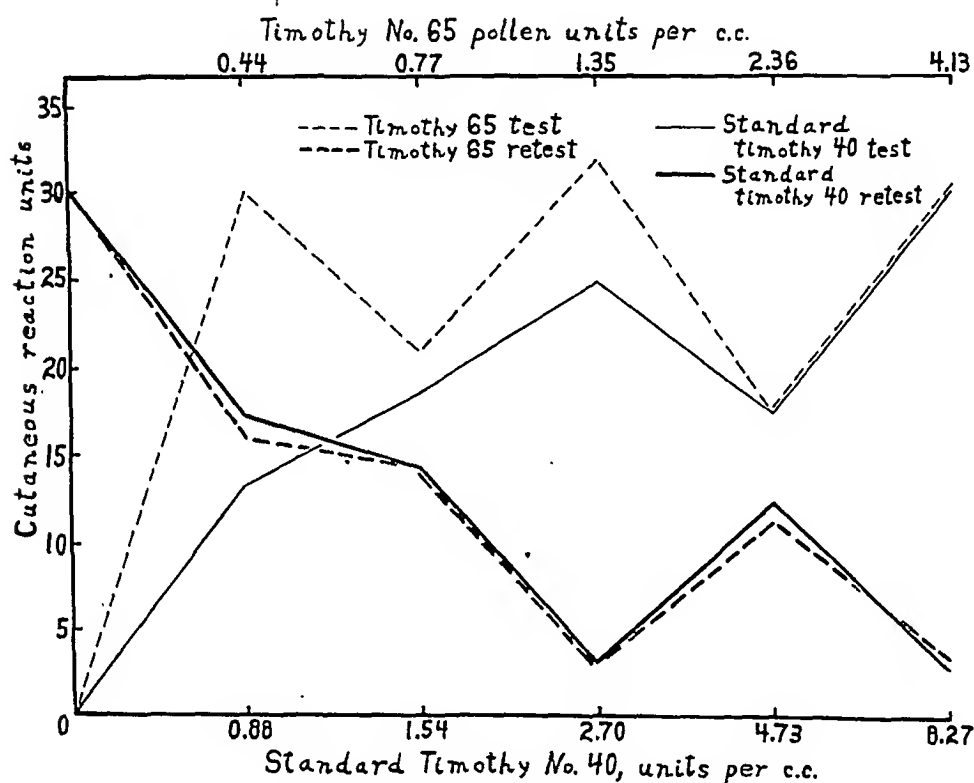


Fig. 12. As in Figure 11, except that the dilutions of timothy No. 65 are one-half those of the standard, as in Table XIII.

arm sites, which were used for the standard series. The retest reactions repeated these rather faithfully, suggesting that they were due to variations in site sensitivity rather than to antigen-reagin reactions. Consequently, this trial had to be largely disregarded. It did, however, show more neutralization in the No. 65 sites than in the No. 40 sites. It also showed that the antigen concentrations had been set too high for this serum concentration, since both extracts gave complete neutralization at 10.03 units per cubic centimeter, rendering the last two sites valueless. From the last

reactions, at 5.73 units, it was estimated that neutralization would probably take place at about 8.27 units per cubic centimeter.

This adjustment was made, keeping both solutions the same, and the trial repeated (Table XII, Fig. 11). - In this trial the timothy No. 40 retests were rather consistently above those of No. 65 by a little more than one step in the series. This was best seen by making a tracing of the upper curve and shifting it horizontally to the left until it came as nearly as possible to coinciding with the lower curve. It then was found to occupy a position a little more than one step in the 1.75 series, corresponding to about one-half the unit strength of its present position. In other words, timothy No. 40 had about one-half the neutralizing power of timothy No. 65. This was put to the test by diluting timothy No. 65 to one-half of the unit strength of timothy No. 40 and repeating the trial (Table XIII). It was seen that the corresponding reaction values of the retests were the same, or nearly so, in all cases and when the curves were plotted (Fig. 12) they virtually coincided throughout. Timothy No. 65 thus was shown to be double the antigenic strength of timothy No. 40.

The reason for the different strengths of the two extracts is not known. The experiment is cited only to show the procedure that is necessary in replenishing or replacing an old standard. Presumably such a difference would not be encountered often under standardized procedures.

#### SUMMARY AND CONCLUSIONS

The physiologic measure of the potency of a pollen extract is deemed to be its ability to neutralize its homologous reagin in human serum.

If a reference standard of dry pollen is maintained and extracts made from it at stated intervals by standardized procedure, they may be used to standardize working extracts of unknown potency by comparing their reagin-neutralizing capacities.

The method employed is *in vitro* neutralization of reagin at local passive transfer sites by dilutions of the standard extract and compared with corresponding dilutions of the working extract. The extent of the neutralization is revealed by retesting the sites with standard pollen extract.

The potency of the standardized extract is expressed in terms of the nitrogen units of the standard extract. Since the potency found for the working extract is that of a dilution of the standard having equivalent reagin-neutralizing value, the unit, as applied to the working extract, is one of reagin neutralization.

This method of standardization is the application of immunologic principles evolved since the discovery of local passive transfer by Prausnitz and Küstner in 1921 and expounded in the works cited below, and to which the writer is entirely indebted.

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(Continued on Page 348)

# PHYSIOLOGIC AND ANTIBIOTIC THERAPY OF INTRACTABLE BRONCHIAL ASTHMA

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## INTRODUCTION

THE intention of this paper is to present recent experience in the use of physiologic and antibiotic therapy in the treatment of intractable asthma. It should be emphasized, however, that every case of asthma requires careful investigation to determine if possible a specific allergic basis for the condition. Seasonal exacerbation of bronchial spasm is only one of the many points in the patient's history that needs inquiry; thus, the incidence of increasingly severe asthma in some patients in the late fall, after the pollen season, at times is due to the unsuspected circulation of dust from boxed-in radiators when the steam heat is first turned on. In houses with central hot-air heating, dust which has accumulated for years in never-cleaned ducts may be blown into the room through perforated grills in the floor. Food and drug sensitivity should be investigated through the patient's history and later by elimination diets. Every effort should be made to track down the multiple allergic factors which may be involved before physiologic or antibiotic therapy is contemplated.

Intractable bronchial asthma develops in patients who respond to epinephrine, either by hypodermic injection or by inhalation of the nebulin, with only partial and transient relief of bronchial spasm. Many of these patients are successfully controlled for a while by administration of aminophyllin. However, the persistence of allergic stimuli in both extrinsic and intrinsic asthma frequently is responsible for a break through of persisting bronchial spasm, despite continued use of both of these bronchodilator drugs. More and more patients with intractable asthma are observed who have become refractory equally to epinephrine and aminophyllin. They require the employment of methods for bronchial relaxation which permit the gradual curtailment of these bronchodilator drugs (epinephrine and aminophyllin), in order that the patient again may become responsive to them.

## PHYSIOLOGIC THERAPY

Of the various methods available, a combination of continuous inhalation of 50 to 70 per cent oxygen and administration of demerol and iodides is the most feasible. Oxygen therapy by means of a ventilated tent, or a rubber catheter inserted in the nasal or oral pharynx, not only

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Presented before the American College of Allergists, San Francisco, California, June 29, 1946.

This study is part of an investigation supported by funds from the Josiah Macy, Jr., Foundation, and, in addition, by a grant from Mr. Cornelius V. Crane, for which the authors wish to express their sincere appreciation.

prevents anoxia but frequently results in a progressive diminution of the severe overinflation of the lungs that characteristically develops in patients with intractable asthma. The diminished pulmonary ventilation engineered by inhaling oxygen-enriched atmospheres gradually permits a more complete emptying of the distended lung, which in itself handicaps the activity of bronchodilator drugs. Saturated solution of potassium iodide in doses of 3 to 4 c.c. daily results in an increased production of mucus, prevention of crusting and, in many instances, a lessening of the allergic state itself.

Intravenous injection of glucose at times is of special value, such as 1,000 c.c. of 5 per cent glucose by slow drip, twice daily. Aminophyllin, 0.5 to 1.0 gm. or more, may be introduced into this solution.\* In some patients, 50 c.c. of 50 per cent glucose, or 200 c.c. of 10 per cent glucose, appears to exercise a therapeutic effect because of hypertonicity as well as its glucose content.

The most successful drug now available for bronchial and central nervous system relaxation when refractoriness has developed to epinephrine and aminophyllin, in our opinion, is demerol. The hazard of respiratory failure is sufficiently great to indicate the abandonment of morphine and its derivatives with most patients. At times, however, dilaudid may be resorted to if scrupulous care is given to limit the dose, such as 1 mg., by hypodermic injection two or at most four times daily for a limited period of two to four days. In 300 patients in whom we have employed demerol, no instance of physical addiction, respiratory depression, or intestinal atony has been encountered. In one of this series, psychic addiction to the drug by a patient with marked psychoneurotic tendencies became a difficult problem; in contrast to this isolated case, many patients have received remarkable benefit from its judicious administration. For patients with recurrent intractable asthma, demerol, therefore, is considered more suitable than any of the morphine derivatives.

The technique of administration is of prime importance in order to avoid side effects which initially may prejudice the patient against its use. Although the dose for an adult is 100 mg. by hypodermic or oral use, the first injection should be limited to 50 mg. since this amount is much less apt to produce dizziness, nausea, and vomiting. When a therapeutic effect is obtained with half the standard dose, it may be repeated at six to eight hour intervals, as indicated, to control paroxysms of bronchospasm. If a larger dose is required, succeeding injections may consist of 75 mg. and finally 100 mg. In the majority of patients observed in our clinic, an injection of 50 mg., followed in one hour by a second dose of 50 mg., is more apt to produce maintained bronchial and central nervous system relaxation without dizziness and nausea than a single injection of 100 mg. When the patient lies as quietly and in as recum-

\*This procedure was advocated by Goodall and Unger recently (American College of Allergists, San Francisco, California, June, 1946).

bent a position as possible for two hours after administration of demerol, side effects are much less common. (The benefit derived from complete rest after administration of large doses of aminophyllin also is appreciated by the patient when it is explained to him that side effects are far less likely to take place.)

In substituting demerol for aminophyllin and epinephrine, the co-operation of the patient should be obtained by previous explanation of the purpose of the program, namely, to restore sensitiveness to drugs that he formerly relied upon, by a temporary period of relinquishing their use. Additional sedation frequently is necessary and generally is best obtained with phenobarbital in doses of 0.1 to 0.2 gm. by mouth or by hypodermic injection. After a course of five to seven days of repeated administration of demerol, iodides, and oxygen, the dose of demerol may be reduced and limited gradually to nighttime administration. For patients who respond favorably, oxygen then is stopped and potassium iodide is reduced to 0.5 c.c., two to three times daily.

For patients with more persistent bronchial spasm, the cumulative effect of repeated inhalations of 75 to 80 per cent helium with 25 to 20 per cent oxygen produces, at times, a satisfactory remission. If experienced technical supervision is available, this gas may be administered with the pressure hood under a positive pressure of 3 to 6 cm. water for periods of two to three hours, three or four times daily, for a period of four to five days. For many patients it will be found simpler to use the Meter mask with the inspiratory disc, for the inhalation of an 80 per cent helium and 20 per cent oxygen mixture, one-half to one hour, four to eight times daily.

Demand regulators, developed during the war for continuous and intermittent positive pressure which was used to combat the anoxia of high altitude flight, soon will be available for clinical use, for the administration of both helium-oxygen mixtures and 100 per cent oxygen. Positive pressure respiration with both 100 per cent oxygen and helium-oxygen mixtures reduces the pathologically elevated, negative intrapulmonary pressure during the inspiratory cycle and accomplishes a substantial relief of dyspnea and, in that way, facilitates the withdrawal of bronchodilator drugs and achievement of a satisfactory remission. These measures have been employed in a program of physiologically directed therapy of intractable asthma.<sup>2,3,4,20,21</sup> An injector has been added to the expiratory pressure wash which now provides inspiratory positive pressure as well; this is of great help in the treatment of asthmatic dyspnea.

Continuous nebulization of 1 c.c. of 1 per cent neosynephrine followed by 1 c.c. of 1:100 epinephrine at times is of considerable value. The combination of nebulized epinephrine and neosynephrine solutions with inhalation of a helium-oxygen mixture generally produces better bronchial relaxation than nebulizing them with pure oxygen.<sup>28</sup> The Meter



mask may be employed with the inspiratory disc removed, the nebulizer being attached to the oxygen inlet of the mask; the carburetor opening of the nebulizer is closed tightly with a cork after instillation of the solution. A flow of 4 to 6 liters per minute of the helium-oxygen mixture is used to nebulize the bronchodilator solutions. It may be remembered that a specified liter flow on the oxygen regulator results in a delivery 1.7 times greater than when it is attached to the helium-oxygen cylinder, since the velocity of movement of a gas through a narrow orifice is inversely proportional to the square root of the density of the gas, which is itself an illustration of its effect in clinical bronchial obstruction. An additional advantage of nebulizing bronchodilator and bronchovasoconstrictor solutions with helium and oxygen is that this gas may diffuse into areas of the lung impervious to air or oxygen alone, thus achieving more efficient alveolar ventilation and penetration of the nebulin to smaller bronchial passageways. The use of these aerosols two to four times daily frequently results in cough and the expectoration of mucoid or mucopurulent sputum.

In patients with pulmonary emphysema, the conspicuous manifestations of bronchial spasm frequently have been erroneously diagnosed as bronchial asthma. It is of considerable importance to make the distinction between uncomplicated bronchial asthma and pulmonary emphysema. In patients who are studied under the fluoroscope, the impaired movement of the flattened diaphragm is manifest in those with organic pulmonary emphysema, even in the absence of wheezing respiration. Patients with pulmonary emphysema (in the absence of an exacerbation of bronchial spasm) generally give the history of being able to assume the recumbent position without increase of dyspnea. Shortness of breath on exertion may occur in both conditions, but in patients with pulmonary emphysema, dyspnea on exertion rather than at night is characteristic, whereas in patients with asthma, nocturnal paroxysms are present almost universally. The distinction in diagnosis is of special importance in treatment.

Patients with pulmonary emphysema who are treated with complete rest in bed and demerol administered by mouth, 50 mg. three times a day and 50 mg. at bed time, frequently will manifest more or less complete freedom from the persistent bronchial spasm previously present. Hypodermic use of demerol may be employed in patients with pulmonary emphysema, but it is noteworthy that ingestion of the drug often is effective, whereas in patients with bronchial asthma, hypodermic injection generally is required. The better response of the patient with organic pulmonary emphysema to treatment with rest in bed and demerol, or rest in bed, demerol, and inhalation of oxygen, may be traced to the absence of a high pathologically elevated intrapulmonary pressure. In such a patient, intrapleural pressure approaches that of the atmosphere during both inspiration and expiration, due to loss of the elastic elements in the pulmonary parenchyma. Although refractoriness does develop to

ephedrine, aminophyllin, and nebulized epinephrine in patients with pulmonary emphysema, restoration of sensitiveness to these drugs is accomplished satisfactorily by physiologic therapy in a considerable number of patients. However, in patients with pulmonary emphysema in whom marked overinflation of the lungs is present, physiologic therapy must include longer periods of oxygen treatment with accessory measures, such as manual elevation of the diaphragm after a preliminary inhalation of nebulized epinephrine and neosynephrine. This procedure, used by Gay,\* consists of placing the palms of the hands under the lower ribs and pressing them against the abdomen, inward and upward, to raise the leaves of the diaphragm during the latter third of expiration. In a certain number of patients who subsequently do not trap air quickly, ten to fifteen manual elevations of the diaphragm may result in a vital capacity of 200 to 1,000 c.c. greater than that present prior to this measure.

Miscellaneous procedures employed in intractable asthma will be referred to briefly. Anesthesia with ether at times is successful if deep relaxation is accomplished by inhalation of the gas for a period of forty minutes, or by rectal administration, such as 75 to 90 c.c. of ether mixed with an equal amount of olive oil.<sup>16</sup> The patient always should be attended following ether anesthesia, the head of the bed lowered, and the patient turned on his side with the face turned downward on the pillow. A pharyngeal airway, inserted after the anesthesia, may be allowed to remain in the mouth until the patient becomes conscious, when it is removed. The administration of oxygen by nasal catheter frequently is useful. Bronchoscopy under ether is often life-saving in patients past middle age, since *thorough* aspiration of mucus which cannot be expectorated may be followed by termination of the asthmatic state. The procedure seems safer and more effective when ether anesthetic is used than cocaine locally.

In patients with abundant expectoration, fever therapy generally is preferable to ether anesthesia. Good results also are obtained with fever therapy in patients with prolonged bronchial spasm and minimum expectoration.<sup>24</sup> Of eight patients recently treated in a hyperthermia cabinet with a temperature of 103° F. to 105° F. for three hours, four obtained a highly satisfactory remission, two were improved, and two were unchanged. Although mild or moderate attacks of asthma may recur two weeks to two months following fever therapy, the patient generally is able to control these symptoms adequately by inhalation of nebulized epinephrine or with aminophyllin by mouth.†

Although a remission may be obtained by one fever therapy, two or three additional exposures to fever at intervals of two to three days are

\*Gay, Leslie: *Diagnosis and Treatment of Bronchial Asthma*. Baltimore: Williams and Wilkins, 1946.

†The Vaponefrin nebulizer produces particles of small size. The Vaponefrin solution which consists of a 1:75 concentration of levo and dextro-rotatory epinephrine also has been found more suitable in our experience than other varieties of 1:100 epinephrine.

more likely to result in a satisfactory remission. Artificial fever also is induced conveniently by the intravenous injection of 0.3 c.c. triple typhoid vaccine mixed with 1,000 c.c. normal saline or 5 per cent glucose, administered by slow infusion. After a chill has taken place, the infusion may be interrupted for a short period or given more slowly. When the fever is maintained for three hours, better results are obtained than when it is terminated promptly after the chill.

The use of filtered air is worthy of emphasis since new simplified window filters are available. For patients with asthma due to grass or ragweed pollen, residence in a filtered air room is apt to result in prompt relief of hay fever and bronchial spasm. The procedure also is valuable for patients who have had an excessive exposure to dust and are unusually sensitive to it. When rooms are especially equipped for filtered air, the routine precaution of having an allergen-proof cover on the pillows and the mattress should be observed. If a window filter is employed, satisfactory evidence should be available to establish its efficacy in the removal of pollen and dust. In some of the air-conditioning units used before the war inadequate filtration of pollen commonly was observed. The symptoms of hay fever and asthma will be completely relieved only if careful attention to the efficiency of the filtering agent, as well as to its actual use, is carried out. The window filter should have a leak-tight fit and the other windows and the door into the room should be kept closed. Continuous operation of the motor-blower unit is necessary to provide a steady delivery of filtered air into the room and prevent unfiltered air from entering. The removal of pollen and dust may be accomplished without electro-static precipitation.

Air filtering units, which are used commonly during the warm weather, do not provide cooling and dehumidification. However, efficiency in the filtering unit is of greater importance than cooling by an air-conditioner. Subjective comfort generally may be obtained conveniently by an additional fan to increase air movement. An efficient fan within the room combined with filtered air brought in from the outside may be found more satisfactory than the employment of a large air-conditioner, unless the latter is equipped with an unquestionably efficient device for filtration.

#### ANTIBIOTIC THERAPY

The treatment of infectious asthma by antibiotic therapy naturally was stimulated by the successful use of penicillin in the treatment of infection caused by Gram-positive organisms. Many reports, both favorable and unfavorable, now are in the literature concerning the efficacy of penicillin administered by injection and by inhalation as an aerosol.<sup>11,13,14,15,17a,19,23,26</sup> An intensive investigation has been in progress at the Presbyterian Hospital, New York City, for the past three years. The results in sixty patients with asthma have been subjected to study both from the point of view of the immediate effect as well as the follow-up

results. In our experience, the patients who were benefited markedly do not comprise a large group, although significant evidence of the therapeutic value of the drug has been observed in a number of patients. Patients who have purulent expectoration are more likely to respond to antibiotic therapy than those in whom a mucoid sputum without pus cells is present. Penicillin therapy appears to be indicated definitely for patients with an associated chronic bronchitis, bronchiectasis, or sinusitis, and in a certain number of patients in whom bronchial asthma appears in association with bronchial infection and pulmonary emphysema.

The results of penicillin treatment in terms of clinical response, duration of improvement, reactions, and effect on organisms recovered from the sputum culture are shown in Tables I and II. Many of these patients previously had been exposed to physiologic therapy with varying degrees of improvement. In this study the attempt was made to separate effects of antibiotic therapy from the additional course of physiologic treatment that could not be withheld from patients of this type. It will be observed that these patients were treated with penicillin aerosol and in some cases with systemic administration.

Of ninety-one courses of penicillin therapy in sixty patients clinical improvement was marked in sixteen patients, moderate in nineteen, slight in thirty-six, and none in twenty. Improvement attributable to physiologically directed therapy in the same series was considered marked in nine, moderate in fifty-one, and slight in nineteen. Nine patients were unimproved by either type of therapy although previously they had been benefited from physiologic therapy.

Of thirty-five patients who manifested marked or moderate improvement due to penicillin therapy, duration of improvement was over two months in twenty-one and less than two months in fourteen. Of sixty showing marked or moderate improvement due to physiologically directed therapy, improvement was sustained over two months in thirty-nine and less than two months in twenty-one.

Reactions to penicillin necessitating interruption of therapy occurred during twenty-four of the ninety-one courses. Exacerbation of asthma was seen in fifteen patients, urticaria in ten, sore, reddened tongue in seven, and fever and swollen joints in one.

In fifty-five patients from whom sputum cultures were obtained before and after penicillin therapy, forty-one showed disappearance of the original predominating Gram-positive cocci and subsequent predominance of Gram-negative bacilli.

The association of sinusitis with intractable asthma is well known and has been subjected to renewed investigation. Although extrinsic allergic factors may maintain both sinusitis and asthma in many persons, the presence of purulent secretion in the nose, with clinical and x-ray evidence of sinusitis, has appeared to be a proper indication to attempt to

TABLE I. BRONCHIAL ASTHMA TREATED WITH PENICILLIN AND PHYSIOLOGICALLY DIRECTED THERAPY

Case No.	Sex and Age	Additional Diagnosis	Course	Route of Administration* and Total Dosage	Duration of Therapy (days)	Improvement Due to Penicillin Therapy	Improvement Due to Physiologically Directed Therapy	Duration of Improvement	
								Less Than Two Months	More Than Two Months
1	M 36	Pulmonary emphysema, chronic bronchitis	1	I. 1,060,000	9	marked	moderate	+	
2	F 61	Pulmonary emphysema, pulmonary fibrosis	1 2 3	I. 660,000 I. 1,300,000 I.M. 470,000 I. 3,400,000 I.M. 6,426,000	7 7 14 16 11	marked none none	moderate slight none		+
3	F 40	Pulmonary emphysema, pulmonary fibrosis, chronic bronchitis	1	I. 1,400,000	7	moderate	moderate	+	
4	M 52	Pulmonary emphysema, pulmonary fibrosis, cardiac insufficiency	1	I. 840,000	7	slight	slight		
5	F 60	Pulmonary emphysema, pulmonary fibrosis	1 2	I. 2,500,000 I. 2,000,000	8 10	marked marked	moderate slight	+	
6	M 57	Bronchiectasis, pulmonary emphysema, chronic sinusitis	1 2 3 4	I. 1,400,000 I. 2,400,000 I. 1,728,000 I.M. 1,030,000 I. 4,350,000 I.M. 3,180,000	7 21 19 35 12	marked none slight slight	marked moderate slight slight	++ +	
7	F 63	Pulmonary emphysema, chronic bronchitis, chronic sinusitis	1 2 3 4	I. 1,770,000 I.M. 840,000 I.M. 1,230,000 I.M. & S.C. 2,250,000 O. 3,800,000 I. (NS) 300,000 I.M. 500,000	10 7 11 10 9 3 3	moderate slight slight slight	moderate moderate marked moderate	+	
8	M 62	Bronchiectasis, pulmonary emphysema, chronic bronchitis	1	I. 1,040,000	10	moderate	moderate	+	
9	F 42	Pulmonary emphysema, chronic bronchitis, chronic sinusitis	1 2 3 4 5 6	I. 1,500,000 I. 300,000 I.M. 5,392,500 I. 3,000,000 I. (NS) 1,000,000 I. 2,125,000 I.M. 3,400,000 I. 3,000,000	10 3 25 21 10 17 21	moderate slight moderate marked marked moderate	marked moderate slight slight slight slight	+	+
10	M 53	Chronic bronchitis	1	I. 1,050,000	5	marked	moderate	+	
11	F 71	Pulmonary emphysema, chronic bronchitis, chronic sinusitis	1 2	I. 2,050,000 I. (NS) 6,000,000	8 70	marked moderate	moderate moderate		++
12	M 39	Chronic sinusitis, pulmonary emphysema	1	I. 1,600,000 I.M. 800,000	8	none	none		++

## BRONCHIAL ASTHMA—BARACH AND GARTHWAITE

[illegible]

TABLE 1—CONTINUED

Case No.	Sex and Age	Additional Diagnosis	Course	Route of Administration* and Total Dosage	Duration of Therapy (days)	Improvement Due to Penicillin Therapy	Improvement Due to Physiologically Directed Therapy	Duration of Improvement	
								Less Than Two Months	More Than Two Months
30	F 63	Pulmonary emphysema, pulmonary fibrosis, chronic sinusitis, chronic bronchitis	1	I. 3,600,000 } O. 1,800,000 }	9	slight	moderate		+
31	F	Chronic sinusitis, pulmonary emphysema	1	I. (NS) 5,400,000 } O. 7,700,000 }	19	slight	moderate		+
32	M 57	Chronic sinusitis	2	O. 3,300,000	10	slight	moderate		+
33	F 61	Pulmonary emphysema	1	I. (NS) 6,100,000 } I.M. 2,320,000 }	15	slight	moderate		+
34	M 41	Pulmonary emphysema, chronic sinusitis	1	I.M. 1,750,000 } O. 1,600,000 }	12 2	slight	marked		+
35	M 68	Pulmonary emphysema, chronic sinusitis	1	I. (NS) 1,550,000	10	none	none		
36	F 68	Pulmonary emphysema, chronic sinusitis	1	I. (NS) 2,500,000 } O. 2,000,000 }	10	none	none		
37	F 54	Pulmonary emphysema, acute pharyngitis	1	I. (NS) 1,000,000 } O. 15,150,000 }	12 19	none	moderate		+
38	M 10	Pulmonary emphysema, chronic bronchitis	1	O. 5,900,000	9	slight	marked		+
39	M 36	Chronic sinusitis	1	I. 1,000,000 } I.M. 1,160,000 }	8	moderate	marked		+
40	F 57	O	1	I. (NS) 950,000 } I.M. 960,000 }	9 8	slight	moderate		+
41	F 38	Chronic sinusitis, chronic bronchitis	1	I. 2,000,000 } I.M. 1,475,000 }	8 9	moderate	none		+
42	F 57	Pulmonary emphysema	2	I. (NS) 1,000,000 } I.M. 1,120,000 } I. 4,500,000	7 30	slight	moderate	+	
43	M 35	Chronic sinusitis	1	I.M. 650,000	8	none	none		
44	M 14	O	1	I. 2,500,000 } I.M. 2,250,000 }	10 12	slight	moderate		+
45	M 44	Chronic sinusitis, chronic bronchitis	1	I. 800,000 } I.M. 1,550,000 }	8	moderate	marked		+
				I. 1,700,000 } I.M. 1,375,000 }	3 6	moderate	marked		+
				I. (NS) 100,000	2				+

## BRONCHIAL ASTHMA—BARACH AND GARTHWAITE

		Chronic sinusitis	1	I. (NS) 1,850,000	8	marked	moderate		
46	M 13	Chronic sinusitis							+
47	F 36	Pulmonary emphysema, chronic sinusitis, chronic bronchitis, Periarthritis nodosa	1	I. (NS) 4,000,000 } O. 3,000,000 } I.M. 1,500,000 }	23 10 12 10 5	slight none	slight none		
48	M 52	Chronic bronchitis	1	I. 1,600,000	7	slight	moderate		+
49	M 54	Pulmonary emphysema, chronic sinusitis	1	I. 650,000	4	none	slight		
50	F 5	Pulmonary emphysema, pulmonary fibrosis, chronic pneumonitis	1 2	I. 2,800,000 } I.M. 1,600,000 } I. 4,000,000 }	20 13 26	moderate slight	moderate moderate		+
51	F 31	Pulmonary emphysema, chronic sinusitis	1 2	I. (NS) 750,000 } I. (NS) 3,000,000 } I. 1,000,000 }	8 21 10	slight slight	moderate slight		+
52	F 48	Chronic sinusitis, chronic bronchitis	1 2	I. (NS) 1,875,000 } I. (NS) 4,200,000 }	16 90	moderate slight	moderate moderate		++
53	F 62	Chronic sinusitis, pulmonary emphysema	1 2	I. 1,400,000 } I. (NS) 2,000,000 } I. 4,000,000 }	17 20	slight none	moderate none		+
54	F 53	Chronic sinusitis	1	I. (NS) 2,400,000 } I.M. 200,000 }	14 2	none	moderate		+
55	M 57	Pulmonary emphysema, chronic bronchitis	1	I. 1,600,000 } I.M. 675,000 }	8 3	slight	moderate		+
56	F 14	Allergic rhinitis, subacute sinusitis, acute bronchiolitis	1 2	I. (NS) 1,500,000 } I. 1,000,000 } I. (NS) 1,000,000 } I.M. 2,540,000 }	10 10 17	moderate marked	moderate moderate		+
57	M 50	Pulmonary emphysema, chronic sinusitis, chronic bronchitis	1	I. (NS) 3,000,000	19	none	slight		
58	F 35	O	1	I. 1,400,000 } I. (NS) 500,000 } I.M. 600,000 }	10	moderate	moderate		+
59	F 55	Pulmonary emphysema	1	I. 1,000,000	8	slight	moderate		+
60	M 33	Pulmonary emphysema, chronic sinusitis, chronic bronchitis	1	I. (NS) 5,000,000	15	marked	moderate		+

*I	—	Oral inhalation
I.M.	—	Intramuscular injection
S.C.	—	Subcutaneous injection
O	—	Oral ingestion
I (NS)	—	Nasal inhalation with intermittent negative pressure



TABLE II. BRONCHIAL ASTHMA TREATED WITH PENICILLIN AND PHYSIOLOGICALLY DIRECTED THERAPY

Case No.	Course	SPUTUM CULTURES		Remarks	Remarks
		Before Treatment	After Treatment		
1	1	Strep. viridans	0	Few urticarial spots not persisting	Marked improvement previously obtained by physiologic therapy.
2	1	Pneumococcus, type 31	No pneumococcus	0	Improvement lasted 2½ months after first course.
3	2	Strep. viridans	Strep. viridans	0	Later, benefited from sinus treatment with aerosol and negative pressure.
3	3	Strep. viridans	B. pyocyanus	Increased cough at start of inhalations	Recurrence in ten days, but good improvement on continued therapy at home.
3	1	Pneumococcus, type 3	No pneumococcus	0	Marked improvement previously obtained by physiologic therapy.
4	1	Hemol. Strep. viridans	Strep. viridans	0	Marked improvement for one year previously obtained by physiologic therapy. Later, frequent relapses.
5	1	Gram postdiplococci	B. coli	0	Striking improvement in patient previously adrenalin-fast.
5	2	0	0	0	Exacerbation of asthma on sodium penicillin aerosol.
5	3	0	0	0	Re-entered hospital in severe status asthmaticus. Surgical ether anesthesia finally broke status asthmaticus, but moderately severe asthma persisted thereafter.
5	4	0	0	Local at sites of injections (5% glucose with adrenalin used as diluent.)	Chronic bronchial obstruction, bronchospasm and infection. Respiratory invalid.
6	1	Strep. viridans	B. pyocyanus	0	Expired following persistent status asthmaticus less than two years after first course of therapy.
6	2	Strep. viridans	B. pyocyanus	0	Decrease in all symptoms, but patient relapsed after one month.
6	3	B. pyocyanus	B. aerogenes	0	Emphysema largely functional, but severe during status asthma.
6	4	Hemol. B. pyocyanus	Hemol. B. pyocyanus	0	Exacerbation of symptoms following upper respiratory infection, with good response to therapy.
7	1	Strep. viridans	B. coli	Increased cough on sodium salt.	
7	2	Friedlander's bacillus	Strep. viridans	Local at sites of injection (5% glucose and adrenalin used as diluent.)	
7	3	B. pyocyanus	Hemol. B. pyocyanus	Urticaria.	
7	4	B. pyocyanus	B. pyocyanus	Increase in asthma.	
8	1	Strep. viridans	0	0	
8	2	Staph. aureus	B. aerogenes	0	
9	1	Strep. viridans	B. coli	0	
9	2	Staph. aureus	B. aerogenes	0	
9	3	Ycasts	0	0	
9	4	0	0	0	
9	5	0	0	0	
9	6	0	0	0	
10	1	0	No gram pos. organisms	0	

# BRONCHIAL ASTHMA.—BARACH AND GARTHWAITE

11	1 2	Hemol. Staph. aureus Strep. viridans	Gran. neg. bacillus 0	0 0	Previous course of I.M. penicillin ineffective. Further improvement in all symptoms on treatment with negative pressure.
12	1 2	B. coli Strep. viridans	0 0	0 0	Increased cough on aerosol. Later had surgical ether anesthesia, for persistent intractable asthma, with temporary improvement.
13	1	Pneumococcus, Staph. albus Strep. viridans	0	0	Intereurent acute infection subsided, but asthma unimproved.
14	1 2	Strep. viridans 0	0 0	0 Increased asthma.	Marked initial improvement with relapse later. Exacerbation of asthma.
15	1	Strep. viridans	B. aerogenes	0	Sinusitis unimproved following irrigations and antral instillations of penicillin solution.
16	1	Strep. viridans Staph. aureus	B. aerogenes	0	Reddened sore throat on sodium penicillin aerosol; but no reaction to calcium salt. Asthma subsided, but sinusitis unimproved.
17	1	0	B. coli	Increased asthma, exfoliative dermatitis.	Initial marked improvement with recurrence of asthma due to penicillin or sulfonamido sensitivity.
18	1 2	Strep. viridans 0	B. aerogenes 0	0 0	Emphysema largely functional, but severe during status asthma. Marked improvement in asthma with clearing of sinusitis.
19	1 2	Strep. viridans Strep. viridans	B. aerogenes B. coli B. aerogenes	Increased cough on sodium salt. Soreness at injection sites (with adrenalin added to penicillin.)	Relieved of status asthma, but moderate asthma persisted.
20	1 2	Pneumococcus, type 19 Strep. viridans Strep. viridans B. proteus	B. aerogenes 0	Local at injection sites (5% glucose with adrenalin used as diluent.)	Relieved of status asthma, ambulatory, but asthma persists. Emphysema largely functional.
21	1	Strep. viridans	B. aerogenes B. coli	Local at injection sites (5% glucose with adrenalin used as diluent.)	Asthma persists, but improved.
22	1 2 3	Strep. viridans Strep. viridans Non-hemol. Strep.	B. coli B. aerogenes B. coli	Urticaria, fever, exacerbation of asthma. Sore, reddened tongue, exacerbation of asthma. Increased dyspnea and wheezing.	Asthma persists, but improved.
23	1 2	Strep. viridans 0	0 B. aerogenes	Sore, reddened tongue on calcium penicillin aerosol. Urticaria from I.M. penicillin developing one month after therapy stopped.	Aggravation of asthma following acute bronchitis. Died two months later from bronchogenic carcinoma with metastases.
24	1	Hemol. B. aerogenes Staph. albus	B. aerogenes B. coli	Urticaria and exacerbation of asthma.	Asthma persists, but improved.
25	1	Strep. viridans	0	0	Striking decrease in cough, expectoration, and wheezing. Increase in vital capacity.
26	1	Strep. viridans	B. aerogenes	Exacerbation of asthma.	Oxygen and helium inhalations combined with usual broncho-dilator drugs afforded chief relief. Breathing exercises helped moderately.
27	1	Strep. viridans	B. aerogenes	Nausea from oral penicillin.	Slight and temporary relief from bronchial relaxation. Fever therapy with triple typhoid vaccine broke status asthma; occasional attacks controlled by broncho-dilator drugs.

TABLE II—CONTINUED

Case No.	Course	SPUTUM CULTURES		Remarks	Remarks
		Before Treatment	After Treatment		
28	1	Strep. viridans	Strep. viridans	Soreness at injection sites (adrenalin added to penicillin.)	Asthma less severe following control of infection.
29	1	Strep. viridans	0	0	Urticaria, most marked at injection sites.
30	1	Strep. viridans	B. aerogenes	0	Chief benefit was from physiologic therapy.
31	1	Pneumococcus type 19	B. coli	0	Sinusitis unimproved by x-ray, although symptomatically improved.
32	2	Hemol. B. coli	Hemol. B. coli	0	Asthma remained improved for one year.
33	1	Non-hemol. Strep.	B. aerogenes B. coli	Penicillin reaction manifested by increased cough, severe asthma, fever to 105°, urticaria swollen tender joints.	Asthma markedly improved following fever.
34	1	Strep. viridans	Strep. viridans	Nausea from oral penicillin. Local reaction of soreness, redness, and vesicle formation at injection sites.	Sustained improvement from physiologic therapy, including helium.
35	1	Strep. viridans	B. coli	Increased wheezing following inhalations.	Symptoms controlled on penicillin but returned when therapy stopped. Previously responded well to physiological therapy.
36	1	Strep. viridans Hemol. Strep. B. alkaligenes	B. aerogenes 0'	Increased wheezing following inhalations.  Sore, reddened tongue.	Some control of infection but no improvement in asthma.
37	1	Strep. viridans	B. aerogenes	0	Intractable asthma responded to physiologic therapy despite no improvement in sinusitis on penicillin therapy.
38	1	Hemol. Staph. aureus	0	0	Intractable asthma responded for several months to filtered air prior to use of penicillin. No bronchodilator drugs required after fifth day.
39	1	0	0	0	Rapid improvement with subsidence of all symptoms.
40	1	Strep. viridans	B. coli	0	Onset of asthma following intranasal surgery. Had become adrenalin-fast.
41	1	Hemol. Staph. aureus	B. coli	Sore, reddened tongue on aerosol; urticaria, exacerbation of asthma on combined penicillin therapy.	Moderate asthma for eight months subsided on penicillin therapy alone without any physiologic therapy.
42	2	0	0	0	Improvement only temporary.
43	1	0	0	0	No reaction to aerosol alone. Expired in severe status asthmal one month later.
43	1	0	0	Urticaria, soreness at injection sites (adrenalin added to penicillin)	Intractable asthma failed to respond to usual physiologic therapy, filtered air, and ether anesthesia. Finally improved.

44	1	<i>Strep. viridans</i>	0	0	Rapid and sustained improvement.
45	1	0	<i>B. aerogenes</i>	0	Repeated sinus surgery and irrigations in past with improvement in sinusitis but no relief of asthma.
46	1	0	0	0	Rapid and sustained improvement.
47	1	<i>Hemol. B. pyocyaneus</i>	<i>B. aerogenes</i>	Exacerbation of asthma.	Intractable asthma for three years. Temporary improvement in hospital following fever with bronchial pneumonia. Autopsy diagnosis: Periarthritis nodosa.
48	2	<i>Hemol. B. pyocyaneus</i>	<i>B. aerogenes</i>	Urticaria	
49	1	<i>Strep. viridans</i>	<i>H. influenzae</i>		
		<i>Hemol. Strep.</i>	<i>Non-hemol. Strep.</i>		
			<i>B. aerogenes</i>	Urticaria, exacerbation of asthma.	
50	1	<i>Hemol. Staph. aureus</i>	0	0	Previously markedly improved for three months following I.M. penicillin. Helped mainly by physiologic therapy at present.
	2	<i>Hemol. Staph. aureus</i>	<i>H. influenzae</i>	0	
51	1	0	<i>B. aerogenes</i>	0	Clinical improvement without change in x-rays. Chief benefit from physiologic therapy although penicillin useful in controlling acute infection (organism moderately resistant to penicillin.)
	2	0	<i>Staph. aureus</i>	0	
52	1	<i>Strep. viridans</i>	<i>B. aerogenes</i>	Transient pruritis.	Chief benefit from physiologic therapy. Sinusitis unimproved. Only temporary improvement, chiefly from physiologic therapy.
	2	<i>Strep. viridans</i>	<i>B. coli</i>	Increased asthma	Greater improvement in asthma than sinusitis.
53	1	<i>Strep. viridans</i>	<i>Hemol. B. coli</i>	Sore reddened tongue on calcium penicillin aerosol, and increased cough.	Asthma temporarily aggravated by calcium penicillin aerosol, and also by 15% sodium sulfacetamide aerosol. Inhalations resumed later without reaction.
	2	0	<i>B. aerogenes</i>	No sore tongue using crystalline sodium penicillin aerosol.	Intractable asthma with final refractoriness to all measures. Patient expired.
54	1	<i>D. pneumoniae</i>	<i>B. coli</i>	0	Greatest improvement from artificial fever therapy.
		<i>Staph. aureus</i>			
55	1	0	<i>B. coli</i>	Sore, reddened tongue and throat, increased cough.	Dyspnea and cough provoked by penicillin inhalations. Moderate relief from physiologic therapy.
56	1	<i>Hemolytic Strep.</i>	<i>B. aerogenes</i>	0	Penicillin therapy controlled infection. Asthma improved on combined therapy. No relapse in five months.
	2	<i>D. pneumoniae</i>	<i>B. coli</i>	0	
57	1	0	<i>B. aerogenes</i>	Increased asthma	Dyspnea and bronchospasm became worse on penicillin inhalations, with slight relief from physiologic therapy.
58	1	<i>Strep. viridans</i>	0	0	Marked improvement following artificial fever therapy.
59	1	<i>Strep. viridans</i>	<i>B. coli</i>	Sore, reddened tongue.	Previously had marked improvement with physiologic therapy alone.
60	1	<i>Pneumococcus, type 17</i>	<i>B. coli</i>	Coated brown tongue.	Striking improvement during hospital stay and for few weeks at home. Relapse not helped by occasional inhalations in clinic.
		<i>Staph. aureus</i>	<i>B. aerogenes</i>		

eliminate infection in the paranasal cavities. Although surgical therapy of chronic sinusitis often has been disappointing in accomplishing a recovery from intractable asthma, the relation between infection in the sinuses and the maintenance of an asthmatic state has been confirmed by our studies, in which penicillin aerosol has been used in conjunction with negative pressure in the treatment of sinusitis.

This method of treatment, which has been recently simplified, has been of sufficient value in the eradication of acute, subacute, and chronic sinusitis to justify our recommendation for a widespread trial.<sup>6,7,9</sup> In some patients with intractable asthma, previously treated by oral inhalation of penicillin aerosol without significant benefit, nasal inhalation of penicillin aerosol with repeated negative pressure produced in the antra and other sinuses has been followed by a satisfactory remission of the asthmatic state, coincident with clearing of infection in the sinuses. Four inhalations of 50,000 units of penicillin nebulized by a flow of 6 liters per minute of oxygen are employed generally each twenty-four hours, for a period of ten to twelve days or more. The negative pressure is produced by a flow of oxygen through a venturi tube; when the horizontal arm is connected by suitable tubing to the nose, a negative pressure of 50 mm. Hg has been demonstrated in the antra. When the flow of oxygen is directed through the vertical end of the venturi, penicillin is nebulized and blown into the nasal passages. Intermittent termination of negative pressure in the sinuses is followed by the introduction of a relatively dense mist of penicillin and lodging of the drug on the mucous membrane, as revealed by washings from the antrum following inhalations by this method.

The efficacy of penicillin therapy in bronchial and sinus infections depends on (1) the presence of penicillin-sensitive organisms as etiological factors, and (2) the establishment of a therapeutically active, local concentration of the drug. Following penicillin therapy, Gram-positive organisms disappear from the bronchial and nasal secretions and consistently are replaced by the Gram-negative organisms, *B. coli* and coliform bacteria, *B. pyocyaneus*, *B. aerogenes*, and *B. proteus*. To what extent these organisms were present prior to treatment is difficult to determine, but in more recent studies the search for Gram-negative organisms before treatment has been regarded frequently by isolating them in small numbers. After three to ten days of treatment, these Gram-negative organisms grow in either pure or predominating culture. A favorable therapeutic result may take place in some patients, irrespective of the presence of Gram-negative bacteria. If purulent secretions continue, the failure of clinical improvement appears to be related to the presence of these Gram-negative organisms. As pointed out by Abraham and Chain,<sup>1</sup> Foster,<sup>12</sup> and Meleney,<sup>17</sup> an enzyme produced by Gram-negative bacteria, "penicillinase," may inhibit the bacteriostatic effectiveness of penicillin. In a few instances the colon bacillus may exert a pathogenic action in itself. The use of strep-

tomycin aerosol in combination with penicillin in some patients will result in a successful therapeutic response when penicillin alone has been followed by no alteration in the symptoms. This sequence of events has been demonstrated especially in patients with bronchiectasis, reported by Olsen.<sup>18</sup> In many patients with bronchopulmonary infection, including bronchitis, bronchiectasis, and lung abscess, marked clinical improvement has been observed, even with the persistence in the sputum culture of Gram-negative organisms following treatment.<sup>10,22,23</sup> Other agents, such as 5 per cent sodium sulfathiazole with 5 per cent sodium sulfadiazine, are being investigated as agents to control the growth of Gram-negative organisms when combined as aerosols with penicillin.

Two complications of aerosol therapy need comment. The development of urticaria, which occurs more frequently after penicillin treatment in allergic persons, nevertheless is less common in aerosol sinusitis treatment than in systemic administration. When it does occur, the employment of pyribenzamine is apt to be followed by a satisfactory control of symptoms. The drug may be required in 100 mg. doses four times a day for two to five days, but it is remarkably effective and prompt in the termination of urticaria in the majority of patients. In some instances ephedrine may be employed in combination. The treatment of the patient temporarily is interrupted; when it is thought desirable to continue therapy, a different brand of penicillin or the substitution of crystalline penicillin may permit a second course without development of urticaria. In a few patients in whom severe allergic reactions have occurred, with pains and swelling of the joints, penicillin treatment has been stopped permanently.

The second complication that may occur as the result of aerosol therapy is a reddening or blackening of the tongue. This has been noted previously with the administration of penicillin dissolved in water or in Amphojel and water, even though the concentration of the drug has been under 500 units per cubic centimeter.<sup>5</sup> The tongue and, at times, the throat become not only reddened but sore. In sinusitis treatment, in which nasal inhalation takes place, the occurrence of either a red or black tongue is rare, provided a small hole about  $\frac{1}{4}$  inch is made in the rubber bag, now rarely used; penicillin mist may be delivered to the outside air rather than exhaled through the mouth. In oral inhalation of penicillin the symptoms of tongue irritation are more common. If the mouth is rinsed with water before and during each inhalation and if the throat is sprayed with water from an atomizer before and during the inhalation, the large penicillin particles are dissolved on the moist pharyngeal surface and the complication appears to be less frequent. At times, treatment must be interrupted for two or three days until the tongue resumes its normal color. Just what the mechanism of either blackening or reddening of the tongue is based on has not been determined. In some patients, penicillin aerosol may be inhaled for a period of one year without any noticeable effects on the

tongue; in others it becomes red within two or three days. Some physicians have placed white vaseline on the tongue prior to treatment as a method of avoiding this complication. Tartar on the teeth at times has been observed to be diminished after a course of penicillin aerosol therapy.

Although we have employed 50,000 units of penicillin per cubic centimeter of normal saline or distilled water, using the calcium salt or preferably crystalline penicillin, lower concentrations may be used. If the nebulizer is attached to a Meter mask with the inspiratory disc removed, the patient may breathe penicillin aerosol with oxygen in a mask over longer periods of time at concentrations of 10,000 to 20,000 units per cubic centimeter. Another comfortable method recently used is a hood tent which encloses the head and makes closure at the neck. It is similar to the open top tent, except that the roof of the hood is closed over.

With the glass mouthpiece aerosol rebreathing apparatus,<sup>8</sup> blood levels of 0.1 to 0.2 units per cubic centimeter of serum generally are obtained for two hours after the inhalation of 50,000 units of penicillin aerosol. With mask or hood-tent administration, effective blood levels have been found with higher doses, such as 100,000 units per cubic centimeter. In the treatment of pneumococcus lobar pneumonia, lower blood levels are effective, therapeutically, such as 0.03 units per cubic centimeter, obtained after inhalation of 25,000 units per cubic centimeter at two-hour intervals.<sup>22</sup> The administration of penicillin by intramuscular injection has been shown to result in the cure of pneumonia in some patients when administered for a period of twelve to sixteen hours during the day.<sup>25</sup> The maintenance of a therapeutic blood level during the day by five inhalations of penicillin aerosol and, in addition, the local deposition of penicillin particles add to the efficacy of treatment in those patients in whom bacteria grow on a purulent or fibro-purulent membrane not reached by a capillary blood supply. In some instances, a retiring dose of penicillin has been given either by mouth or intramuscular injection.

In many patients a course of twelve days to two weeks has been used in the treatment of bronchial asthma, with a daily dose of 250,000 units administered as an aerosol; the precise indication for length of treatment is determined by the clinical condition of the individual patient.\* In patients with bronchiectasis, penicillin therapy occasionally has been maintained for a period of a year. The nature of the infection, the penicillin sensitivity of the predominating organism determined by culture of the sputum, the presence or absence of Gram-positive organisms, and many other factors must be taken into consideration before appraising the indications and duration of antibiotic therapy.

The frequency of recurrence of asthmatic symptoms in patients who responded favorably to antibiotic therapy led to the subsequent use of weekly injections of catarrhal vaccine and dust. It has been our impres-

\*Intramuscular injection of the drug is now preferred to avoid the wheezing which may be caused by inhalation of penicillin mists, unless highly resistant organisms are present.

sion that patients, to whom follow-up treatment was given with the standard procedures employed in desensitization with dust and stock vaccine, have fared much better, in terms of maintained improvement, than patients to whom a single or several courses of penicillin have been given without attempts to increase the immunologic and allergic resistance of the patient. Furthermore, this hyposensitization program also would seem to be of value for patients with bronchial asthma who have been treated for sinus infection.

#### SUMMARY

A report is presented on the effectiveness of physiologic and antibiotic therapy in severe or intractable bronchial asthma.

In patients who develop refractoriness to epinephrine and aminophyllin, temporary curtailment of the use of these bronchodilator drugs and substitution of other measures are required to obtain a remission from intractable asthma. The effective administration of demerol, generally in conjunction with continuous inhalation of 50 per cent oxygen, is the simplest program to terminate a state of persistent bronchial spasm. Intravenous injection of isotonic or hypertonic glucose often is a helpful adjunct. Physiologic therapy also includes helium-oxygen inhalations, positive pressure respiration, ether anesthesia, bronchoscopy, and artificial fever therapy for patients who do not respond to simpler measures.

Antibiotic therapy for bronchial asthma by administration of penicillin, either intramuscularly or by aerosol, has a limited although unquestionable value in selected cases. The repeated introduction of penicillin aerosol into the paranasal sinuses, following the release of a previously established partial vacuum, has been followed by clinical recovery in acute, subacute, and chronic sinusitis and, in some instances, with clearance of the symptoms of intractable asthma.

Of ninety-one courses of penicillin therapy in sixty patients with severe bronchial asthma, clinical improvement was marked in sixteen, moderate in nineteen, slight in thirty-six, and absent in twenty. The duration of improvement in thirty-five patients who were moderately or markedly benefited was over two months in twenty-one and less than two months in fourteen. In sixty patients who manifested marked or moderate improvement as a result of physiologic therapy, improvement was sustained over two months in thirty-nine and less than two months in twenty-one.

More sustained improvement after antibiotic penicillin therapy in the treatment of bronchial and sinus infection appears to take place in patients in whom hyposensitization therapy with catarrhal vaccine and dust is instituted directly after treatment and continued for an indefinite period.

Further studies are required to determine the role of Gram-negative organisms which appear subsequent to penicillin therapy in cases of bronchopulmonary and sinus infections. Current investigations of strep-



tomycin and sulfadiazine and sulfathiazole aerosols point to the possibility that patients with mixed infection unresponsive to penicillin therapy may be benefited by antibiotic treatment effective against both Gram-positive and Gram-negative bacteria.

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## MANAGEMENT OF BRONCHIAL ASTHMA

### The Use of 1-(3, 4'-Dihydroxyphenyl)-2-isopropylaminoethanol

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IT is the purpose of this report to enlarge upon our original observations<sup>16</sup> regarding a new sympathomimetic amine,\* (1-(3, 4'-Dihydroxyphenyl)-2-isopropylaminoethanol,  $(\text{HO})_2\text{C}_6\text{H}_3\text{CHOHCH}_2\text{NHCH}(\text{CH}_3)_2$ , which appears to be particularly effective in relieving the dyspnea of an asthmatic attack. Sympathetic amines elicit body responses which simulate those resulting from stimulation of adrenergic nerves, but the location and intensities of these responses differ widely. As far as we know, these are the first reports on this effective pneumodilator in this country.

During the war years, sparse reports from Europe<sup>8,9,10</sup> on the use of this drug, known there as "Aleudrin," became available. It was effective in the control of asthma when used as a simple spray and it furthermore quickly stopped the experimental dyspnea crises induced in healthy subjects by choline aerosols. Experimental work also indicated<sup>11,15,22</sup> that the relaxing action of this drug on bronchial spasm, induced by pilocarpine, was ten times greater than that of epinephrine. Although the drug does not fundamentally alter the basic physio-pathologic condition of bronchial asthma, it is a valuable adjunct in the armamentarium of therapy for this distressing condition.

#### TECHNIQUE EMPLOYED

The value of the inhalation of therapeutic aerosols can be appreciated if one recalls the tremendous absorptive powers of the inner surface of the lung whereby an inhaled medicament almost immediately reaches the desired objective and is not partially dissipated in a circuitous circulation which itself may not be functioning properly. With these aerosols it is possible to obtain high local concentrations and varying blood levels. During the past few years this therapy has gained impetus from the many new drugs which have become available, notably penicillin aerosol with its proven efficacy in conditions formerly resistant to medical treatment.<sup>1,2,3,7,17,18</sup>

The effects of 187 inhalations of Isuprel in eighty-two ambulatory patients with chronic bronchial asthma were studied. Forty hospital patients with severe bronchial asthma were treated and more than half have been followed for varying periods after discharge from the hospital. In the latter group the subcutaneous and oral routes were also employed but the inhalatory route was used far more than the others. The vaponefrin<sup>14</sup>

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\*Isuprel—This work was aided by a grant from Frederick Stearns & Company.

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nebulizer\* was used in all cases and a length of rubber tubing connected it with a regulator attached to an oxygen tank. Oxygen flows of four to five liters were usually sufficient to aerosolize 1.0 c.c. of the Isuprel solution in ten minutes. The subcutaneous route, with solutions of 1:1000, 1:5000 or 1:10,000, was generally used only to initiate the treatment of the acute attack. When the acute attack had been successfully combated, the inhalatory route, alone or in conjunction with the oral, proved adequate. Some of the earlier patients were treated with amounts later shown to be inadequate. Had they been treated with the later established optimum doses their improvement would have been much greater. Also, since the preliminary report, the 1:100 dilution has not been available for nebulization in the follow-up of discharged patients or the treatment of new admissions. A solution of one-half this strength has been used, which has not been as effective. In general, 1.0 c.c. of 1:100 dilution by the inhalatory, 0.2 to 0.3 c.c. of the 1:1000 dilutions by the subcutaneous, and 5 to 10 mg. by the oral route, every three to six hours, gave the best results.

The term "bronchospasm" is used to denote that narrowing of the bronchi and bronchioles which leads to the difficulty in breathing manifested by typical wheezes, squeaks and rhonchi, and by prolonged expiration. This is graded 1+, 2+, 3+ and 4+ and is purely a subjective classification based on the intensity of these sounds from barely audible to extremely loud, the last (4+) being the type heard in the most acute attack.

Vital capacity readings were taken on the McKesson Scott vital capacity apparatus which is convenient because of its easy portability. Many factors enter into any one vital capacity reading which may render it erroneous; e.g., familiarity of the patient with the procedure, age, cough, exhaustion, lack of co-operation, state of dentition, emotions and fear during an attack. However, while certain individual readings may be incorrect when the above factors are involved, it is felt they usually serve as a criteria of a drug's effectiveness and are extremely valuable if taken frequently during a hospitalization period of several days. Widely separated vital capacity readings are very apt to be incorrect, but in most cases the readings taken immediately before and after administration of a drug offer an objective comparison of its effectiveness.

### AMBULATORY PATIENTS

Thirty-nine of these patients were intrinsic asthmatics, twenty-nine extrinsic, thirteen were mixed; four had hay fever and four had chronic bronchitis and bronchiectasis concomitantly. There were forty-two males and forty females, the average age being forty-five years, and ranging from eight to seventy-two years.

Figure 1 illustrates the vital capacity changes for 187 trials in eighty-

\*Obtainable from Vaponefrin Company, Upper Darby, Pennsylvania.

two patients with varying degrees of bronchospasm, employing inhalations of 0.25 to 1.5 c.c. of 1:100 or 1:200 dilutions of isuprel.

As would be expected, the greater the bronchospasm the less the pre-

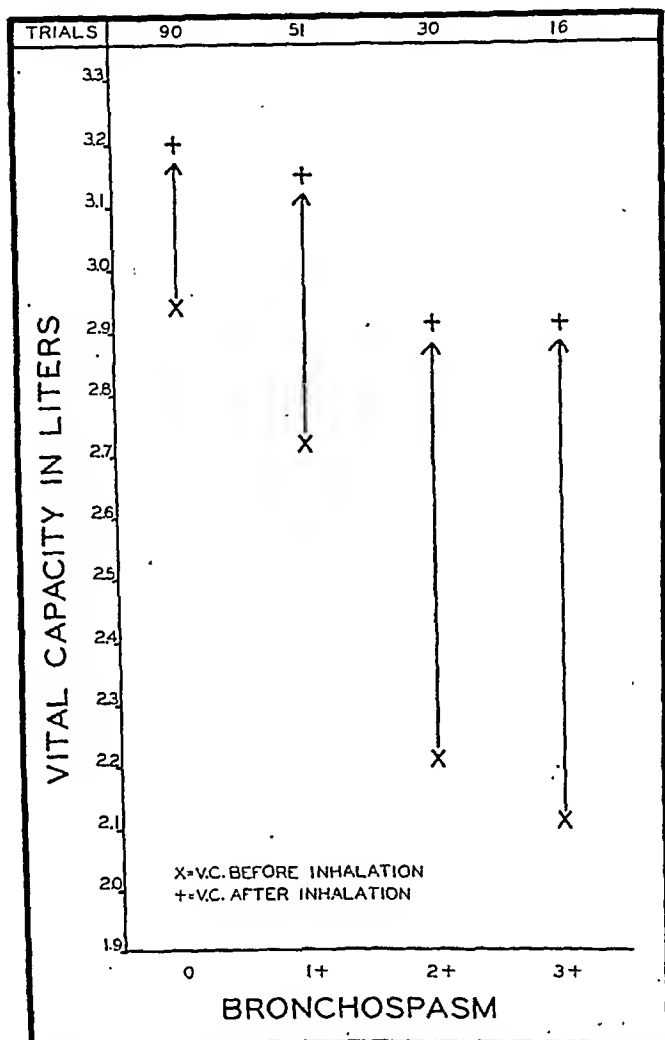


Fig. 1. Averages of 187 vital capacity recordings on eighty-two ambulatory patients with various degrees of bronchospasm using various dilutions (0.25 c.c.-1.5 c.c. of 1:200 and 1:100) of isuprel by oxygen-aerosolization.

treatment vital capacity reading. The average vital capacity of ninety trials in asthmatic patients (Figure 1) without wheezing or rhonchi or prolonged expiration was 2.94 liters, while that of sixteen trials in patients with 3+ to 4+ spasm was only 2.11 liters. The vital capacities in patients with 1+ and 2+ bronchospasm were at proportionate levels. Figure 1 also illustrates that the greater the bronchospasm present, the greater the increase in the vital capacity immediately following a treatment. When no bronchospasm was present, the average increase was only 0.26

liters as compared to 0.43 liters, 0.70 liters, and 0.80 liters, respectively, as the bronchospasm becomes greater.

Figure 2 illustrates the same changes for 134 trials in seventy-four

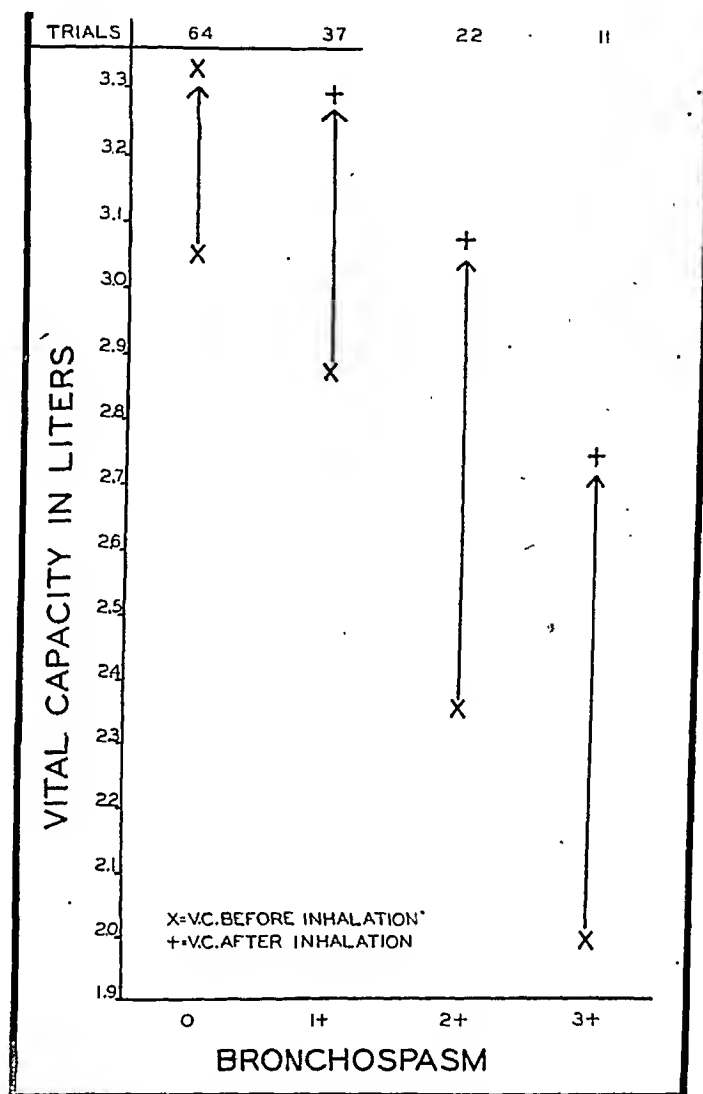


Fig. 2. Averages of 134 vital capacity recordings on seventy-four ambulatory patients with various degrees of bronchospasm using 1.0 c.c., 1:100 isuprel by oxygen-aerosolization.

patients when inhalations of 1.0 c.c. of 1:100 dilutions alone were used.

Figure 3 shows the gratifying response to the drug when the distressing asthmatic cough was present although no physical signs of bronchial obstruction were found. The sixty-four trials shown in Figure 2, where signs of bronchospasm were absent, were done in forty patients. During thirty-seven of these trials, cough was absent; in twenty-seven, the typical, hacking asthmatic cough was present. All were treated by oxygen-aerosolization with 1.0 c.c. of 1:100 isuprel. In those with cough an increase of 0.50 liters was noted, while the other group showed a negligible increase of 0.19 liters. This was particularly surprising since a

persistent cough often results in a poor vital capacity reading. The fact that the pretreatment reading was so low was therefore to be expected, but the swift allaying of the cough which followed inhalation, thereby increas-

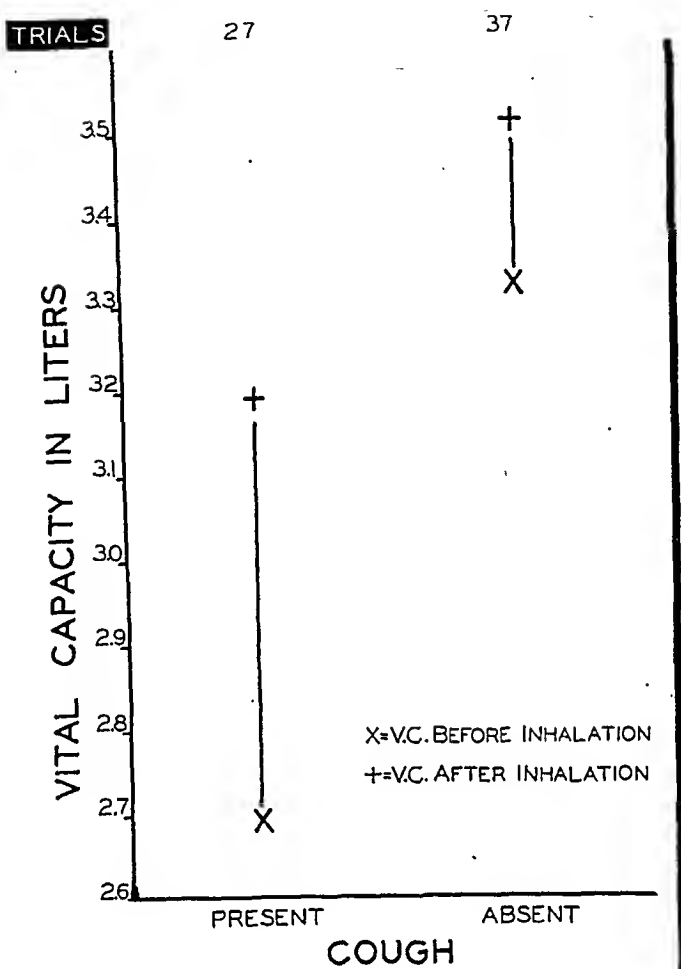


Fig. 3. Averages of sixty-four vital capacity recordings on forty ambulatory patients without signs of bronchospasm using 1.0 c.c., 1:100 isuprel by oxygen-aerosolization, illustrating the effect on asthmatic cough.

ing the vital capacity of these subjects to almost the same level as those without cough, is indeed striking. In addition, several of the ambulatory and hospital patients volunteered the information that expectoration was easier and greater immediately following each inhalation.

#### HOSPITAL-TREATED CASES

Forty hospital patients were treated with this drug alone. Most asthmatics who deserve hospitalization are generally real problems in therapy and the most intensive programs of repeated bronchiolar relaxation<sup>4,5,19,20,21</sup> are necessary to keep them controlled. Such programs require the judicious use of various medicaments, e.g., infusions of glucose, saline or

typhoid, aminophyllin, epinephrine, rectal ether or paraldehyde, positive pressure oxygen or helium-oxygen mixtures and other methods in the first thirty-six to seventy-two hours. However, adequate evaluation of a new drug requires its use alone. Under such circumstances any success may be multiplied somewhat when it is considered how much more valuable the drug will be when used in conjunction with other tried and proved medicaments.

The general program of treatment consisted of 1.0 c.c. of 1:100 dilution every three hours by the oxygen-aerosol technique, omitting one or more night doses, if possible, to allow uninterrupted sleep. The first nine patients were carried on smaller doses than this; nevertheless, all will be considered as a group. Three patients did not receive any inhalation but were treated by oral and subcutaneous routes. One of these was listed as an equivocal result, another as slightly improved, and the third as a failure. Unavoidable factors which at times contributed to irregularity of treatment included an acute shortage of nurses and temporary lack of the drug due to manufacturing difficulties.

The forty hospital patients had a total of fifty-five admissions. A great many were in the severest stage of status asthmaticus when first seen, most having run the gamut of therapy without success before isuprel was tried. Of these, thirty-five were intrinsic, one extrinsic and four were mixed asthmatics. There were seventeen males and twenty-three females, the average age being forty-one years and ranging from thirteen to sixty-nine years. The average duration of asthma was thirteen years, ranging from two to fifty years.

Of the total admissions, eight patients had two admissions, two had three, and one had four. Four of the readmissions were extremely brief and, since they were not treated with isuprel, will be disregarded in the tabulation of results.

Twenty-seven patients during thirty-seven admissions were quickly and markedly improved, seven in as many admissions were moderately improved, three in as many admissions were slightly improved; in one the results were equivocal and two patients with three admissions were classified as failures.

In other words, 85 per cent of the severely ill hospital-treated patients were kept comfortable by this drug alone. In terms of treated admissions, 80 per cent were successful. Since, with one exception, all the cases were either the intrinsic or mixed type of asthma, a notoriously treatment-resistant group, such a proportion of success is most gratifying. In no case did we note resistance to the drug comparable to the epinephrine-fast stage. Of the failures, one (C.J., Case 35) received only two 0.5 c.c. injections of the 1:5,000 dilution subcutaneously among the multiple treatment measures that were employed. All measures failed and she died within forty-eight hours after admission. The other patient who was classed as a failure (L.P., Case 24) was desperately ill during each

of two admissions. During the first he failed to react very dramatically to either the subcutaneous or the inhalatory route. During his second admission bronchoscopy proved to be the life-saving measure. Every two hours for more than forty-eight hours during the critical period of this admission, 0.5 c.c. of the 1:5,000 dilution was injected subcutaneously. This treatment was apparently of benefit, but too many other measures were used concomitantly for accurate evaluation. He was later carried along on nebulization alone and for several months since discharge has done exceedingly well with the use of the hand-bulb nebulizer. Nevertheless, he is classified as a failure.

The three patients classified as "slightly improved" had minimal bronchospasm to begin with and there was not much room for improvement. One has had an excellent course since discharge with no time lost from work as compared with many incapacitating periods and frequent hospital admissions before the inception of this drug. The one "equivocal" result was obtained in a highly neurotic and agitated female. Excellent objective improvement, as manifested by disappearance of cyanosis and quieting of the accessory muscles of respiration, followed 0.33 c.c. subcutaneous injections of the 1:1,000 dilution. However, she would not quiet down until a nasal catheter was inserted, although, unknown to her, the oxygen flow was not turned on. Of the readmissions three were for failure of oral therapy, one was for failure of 1:100 and four were for failure of 1:200 dilution isuprel sprays with hand-bulb nebulizer to control severe attacks. Three occurred in patients who either ran out of isuprel or were not taking it while at home.

#### FOLLOW-UP CARE

Twenty-four patients have been treated following discharge. Due to a limited supply of the drug only the patients with a history of chronic perennial asthma were treated. The likelihood of remission in such cases was minimal and therefore more adequate evaluation of ambulatory management was possible. Five have been followed for less than two months and will not be considered. Several have been treated for six months which is the longest follow-up period. Considering the vagaries of the average asthmatic no definite conclusion can be drawn on the basis of such a short follow-up period. However, definitely favorable trends have been noted.

About half of these patients are employed. All have lost much less time from work than on previous routines of management. It is impossible to estimate this advantage in total dollars and cents but it must be considerable. One patient has been in a sanatorium for six months and has done very well. Only three patients—extremely severe asthmatics with a total of eight hospital admissions—have failed to attain a successful ambulatory regime with isuprel. Two of them, nevertheless, insist that isuprel is more effective than anything they have used.



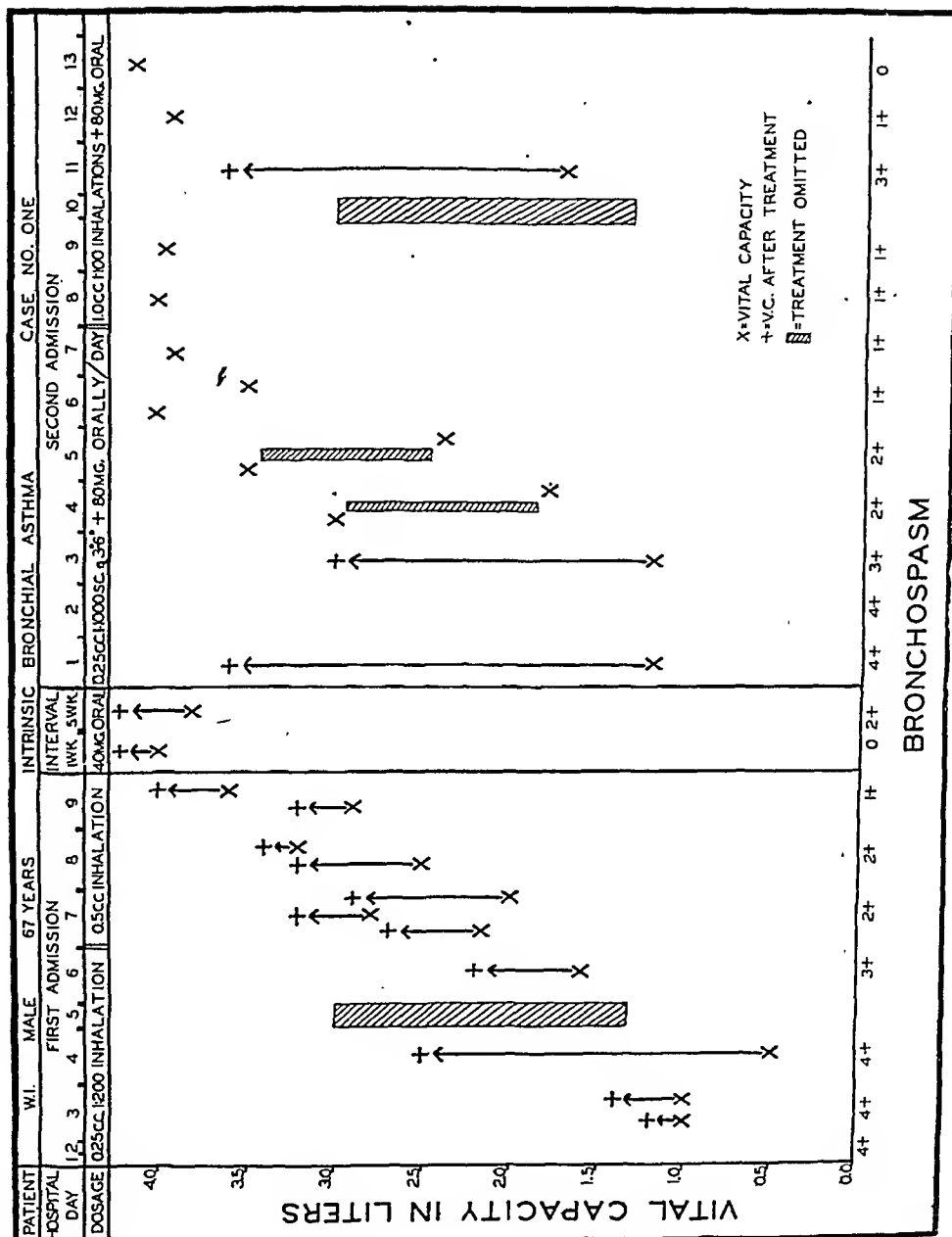


Fig. 4. Vital capacity recordings during two hospital courses (Case 1) treated with isuprel by various routes.

Therefore, 84 per cent of the chronic severe group, which has been followed after discharge from the hospital, have had successful ambulatory courses. Many of the patients had to be changed from the 1:100 to 1:200 solution for hand-bulb nebulization when the former dilution became unavailable. They have noted less effectiveness with the latter, having had to use larger amounts at shorter intervals for adequate control. Brief abstracts of some of the hospitalized cases follow.

#### CASE REPORTS

*Case 1.*—W. I., aged sixty-seven, male, with severe intrinsic bronchial asthma for two years, had been extensively studied and treated allergically with equivocal results. He entered the hospital in status asthmaticus and was given oxygen-aerosol treatment with 0.25 c.c. of 1:200 isuprel (Fig. 4). Though inadequate, this dosage did lead to improvement but it had to be reinforced with other treatment during the first thirty-six hours. After that he showed a regular daily rise in vital capacity readings. Following discharge from the hospital, he took approximately 40 mg. a day orally in divided dosages and maintained a vital capacity of over 4 liters for two months until another severe attack necessitated readmission. During his second admission, he was treated with larger doses from the start and had a smoother course, consistently maintaining a vital capacity above three liters except on three occasions during his thirteen-day stay when isuprel was either temporarily unavailable or inadvertently omitted. The first seven days of his second admission he was also tried on a regime of subcutaneous injections every three to six hours and 10 mg. orally every three hours. This did not control him as well as the oxygen-aerosol technique employed during the last six days, since the effects of the subcutaneous route wore off too quickly. He has been able to return to his work as a janitor, using handbulb sprays of 1:100 isuprel several times daily and 10 mg. orally four times a day. His vital capacity has been maintained at 4 liters for several months since his discharge.

*Case 4.*—B. M., aged twenty-one, female, with a history of chronic asthma for fourteen years and severe asthma for three days, entered the hospital in an epinephrine-fast state. Concomitant nausea, vomiting and unexplained diarrhea contributed to a highly distraught and weakened condition. She had dramatic relief from 0.5 c.c. of 1:1,000 subcutaneous isuprel. Figure 5 shows her subsequent improvement with oxygen-aerosolization of 1.0 c.c. of 1:200 isuprel. When asked to compare this mode of treatment with past routines on previous admissions, she answered enthusiastically that isuprel "worked atomically."

*Case 5.*—A. H., aged eighteen, female, with bronchial asthma for seventeen years, who had been in the hospital more than thirty-six hours without relief in spite of intensive therapy, showed excellent response to 0.5 c.c. of 1:1,000 isuprel subcutaneously. Maintained thereafter on inhalations of 1.0 c.c. of 1:200 dilutions every three hours, she had a progressively good hospital course. She was readmitted briefly a week later because the oral isuprel alone failed to control her. Since discharge she has done exceedingly well by using hand-bulb inhalations once or twice a day, finding them particularly effective during the past six months in aborting all attacks.

*Case 6.*—E. M., aged twenty-six, female, with bronchial asthma for eighteen years, was treated under circumstances almost identical to Case 5 and her hospital course, shown in Figure 5, illustrates both cases for all practical purposes. She, too, had been in the hospital for many hours without relief despite varied treatment, but

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responded immediately to 0.5 c.c. of 1:1,000 subcutaneous isuprel. When technical difficulties obviated oxygen-aerosol during the night, she required another injection to the following morning. Thereafter she showed continued progressive improvement. Both these patients (Cases 5 and 6), with a total of five previous hospital admissions, found isuprel far more effective than previous routines of therapy.

*Case 7.*—G. C., aged fifty-three, male, with bronchial asthma of fifteen years' duration, was seen twenty hours following admission. In spite of intensive therapy, including infusions of saline, or dextrose and saline with aminophyllin, epinephrine subcutaneously, aminophyllin by rectum and luminal, his condition appeared progressively worse. Figure 6 illustrates the immediate excellent vital capacity response to 0.75 c.c. of 1:1,000 subcutaneously and the subsequent improvement on 1.0 c.c. of 1:200 inhalations. *In this patient and in several others the inhalation was repeated immediately, and in this dilution a cumulative effect on the vital capacity recordings was noted.* When ready for discharge, however, he developed a vesicular eruption with crusting around the lips and inhalations were discontinued. Seven hours later he developed another asthmatic attack which resisted epinephrine and aminophyllin injections for thirty-six hours. He was placed on 15 mg. isuprel orally every three hours and showed a gradual improvement during that day. After a few days, some nervousness occurred with this dosage and the dose was subsequently reduced to 10 mg. every three hours. Except for two periods where the drug was inadvertently skipped for nine hours, he manifested progressive improvement as shown by his vital capacity readings.

*Case 11.*—L. M., aged thirty-one, female; entered in extreme status asthmaticus. She had been quite dyspneic for one week but obtained partial relief from aminophyllin intravenously. She accidentally received 20 grains of aspirin at this time and shortly thereafter her attacks became extremely severe. Two years ago she had a similar experience following the use of aspirin and was in status asthmaticus for four days. She was given 20 c.c. aminophyllin intravenously and 0.5 c.c. epinephrine subcutaneously with no response. One-half hour later she was given 30 c.c. of ether in 60 c.c. of oil rectally, and this was repeated in one hour. She continued dyspneic, wheezing and cyanotic and received 1,500 c.c. of 5 per cent glucose in saline with aminophyllin. Four hours following entry there was no appreciable change from the admission picture except a more profound picture of exhaustion. She was given 1.0 c.c. of 1:200 isuprel by inhalation and within a few minutes responded dramatically, breathing much easier. Approximately six hours later she experienced another severe attack which also responded quickly to 0.5 c.c. 1:1,000 subcutaneously. Thereafter, except for marked weakness for twenty-four hours, she improved progressively, with 1.0 c.c. 1:200 every three hours by oxygen-aerosolization. On the fifth hospital day, upon learning that her x-ray showed bilateral tuberculosis, she left the hospital. She was readmitted eleven days later in a moderate attack and this responded quickly to oxygen-aerosolization of isuprel. She spent three and one-half uneventful weeks while awaiting sanatorium accommodations. During this period, and since that time while in the sanatorium, she has been relatively free of acute attacks and more comfortable than she has been in years by the daily use of nebulized isuprel and approximately 60 mg. orally per day in divided dosages. The 1:200 dilution has not been as effective as the 1:100 dilution while in the sanatorium.

*Case 15.*—J. B., aged sixty-six male, with bronchial asthma of four years' duration, had been in the hospital four days. During the previous two weeks at home his asthma had been resistive to all treatment. While in the hospital he continued to have two severe attacks daily with only slight relief from infusions of 0.5 gm. aminophyllin in 1,500 c.c. glucose-saline twice a day. He was started on inhalations

of 1.0 c.c. 1:100 every three hours, with immediate increase in his vital capacity following the first inhalation (Fig. 5). The day and night attacks did not recur. On the fifth day of treatment, because of a continued daily temperature spiking to 101 F., 50,000 units of penicillin were dissolved in each cubic centimeter of isuprel. His vital capacity continued to increase and at time of his discharge was 4.1 liters, which is a higher reading than would have been predicted in a man of his age. Since discharge he has used small amounts by inhalation nightly and occasionally during the day, and for two months has been free of attacks.

*Case 22.*—E. S., aged twenty-one, female, with bronchial asthma and intermittent eczema since birth, has had six lengthy Boston City Hospital admissions during the past three years. For twenty-four hours she was in severe asthma not relieved by four administrations of aminophyllin intravenously and one infusion of 5 per cent glucose in saline. She showed an immediate dramatic response when given 0.3 c.c. of 1:1,000 isuprel subcutaneously. The vital capacity improved from 0.8 liters to 2.4 liters in fifteen minutes and she changed from a wheezing, sick-appearing, sullen, uncommunicative girl to a smiling, talkative, much happier person. The cycle was broken by 0.25 c.c. injections of 1:1,000 subcutaneously every two hours for five doses and then every three hours. This was supplemented with 10 mg. orally every three hours. Forty-eight hours after this treatment she was started on oxygen-aerosol inhalations. In spite of marked irregularity of treatments, she managed to keep very comfortable. Since discharge she has used hand-bulb inhalations of isuprel with better results than were attained from many other drugs formerly used.

*Case 28.*—M. G., aged twenty-two, female, with a ten-year history of bronchial asthma, had frequent lengthy hospital admissions. Her present attack began at 6 p.m. on the day of admission and was not relieved by numerous injections of epinephrine at ten-minute intervals. Her physician gave her aminophyllin intravenously and she lapsed into unconsciousness and became deeply cyanotic. He administered artificial respiration and the fire department administered oxygen. She was then brought into the hospital and started on oxygen by face mask. She received 0.25 gm. aminophyllin intravenously on the admitting floor and arrived on the ward semiconscious and in great respiratory distress. Oxygen-aerosolization of 1.0 c.c. of 1:100 isuprel was administered with almost immediate dramatic relief. Full relief was observed in ten minutes and she had no further dyspnea the remainder of the night. She remained in the hospital for three weeks during which time dental extractions were made. She was completely comfortable on p.r.n. inhalations of isuprel. Since returning home, she has continued her hospital routine of taking small inhalations four or five times a day and 40 mg. orally in divided dosages. She finds this routine is far more effective than the previous home management of her asthma by epinephrine hypodermically.

#### SUBCUTANEOUS ROUTE

The 1:1,000 dilution by the subcutaneous route was studied in fifteen hospital patients. Twelve of these patients had chronic severe asthma and had been without relief in spite of varied intensive therapy over many hours. Eleven of these patients were epinephrine-fast and had been in status asthmaticus from four to seventy-two hours, averaging twenty-nine and six-tenths hours. One patient (Case 1), in his second admission under this program, had in the past failed to react favorably to epinephrine and other treatments when his attack entered the status state. The

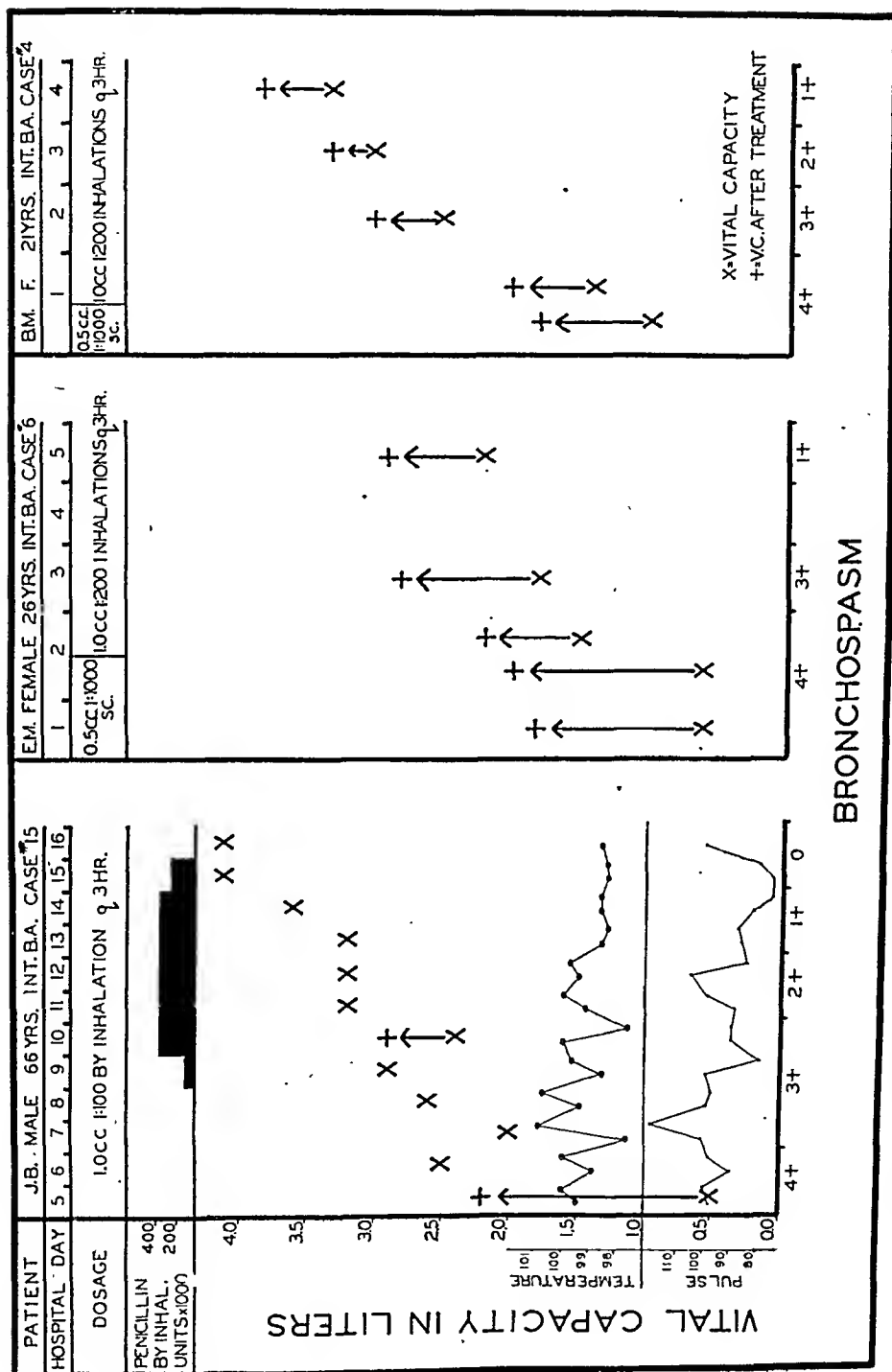


Fig. 5. Vital capacity recordings during hospital courses of three cases treated with isuprel by various routes.

other three patients had been in the hospital for varying lengths of time and, while not in status asthmaticus when treatment was instituted, were real therapeutic problems. The dosage varied from 0.25 to 0.75 c.c., with 0.25 c.c. of the 1:1,000 dilution appearing to give the best relief for dyspnea with the least side effects.

Eighteen vital capacity recordings were made. In each of the eighteen trials, including those for the eleven epinephrine-fast patients, these recordings show that the injection brought marked and immediate relief. This relief was usually noticeable within five minutes and reached its peak in about ten minutes. Figure 7 illustrates the average capacity before and after injections. There was an average increase of 1.18 liters in the eighteen trials, the smallest increase being 0.4 liters and the largest, 2.6 liters. Excluding the three patients not in status asthmaticus, the average increase in vital capacity following injections was 1.4 liters.

Unfortunately, the effects of the subcutaneous route were not long-lasting, and in two or three hours the patients usually required another injection in order to maintain the initial improvement. Its greatest effectiveness frequently appeared to be in breaking up the cycle of status asthmaticus although intensive therapy over the following twelve to twenty-four hours had to be given to retain the gains made. This may be done by repeating the subcutaneous dose every two hours for twelve hours or changing to oxygen-aerosolization of 1.0 c.c. of 1:100 dilutions every two to three hours, or using both, depending on the severity of the bronchospasm. Once the asthmatic cycle has definitely been broken, the patient is best treated with oxygen-aerosolization at gradually increasing intervals until discharge.

Since our preliminary report 0.25 to 0.5 c.c. of the 1:5,000 and 0.5 c.c. to 1.0 c.c. of the 1:10,000 dilutions have been used subcutaneously in seven patients. Although fewer side effects were noted and a moderate transient improvement was usually seen, the results were not as dramatic as those with the 1:1,000 dilution. The latter appears to be most effective in the initial active treatment of the very ill asthmatic who needs hospitalization.

#### ORAL ROUTE

Nine patients are taking oral isuprel in conjunction with hand-bulb inhalations. Most of these patients feel that the drug taken orally is not as effective as by inhalation. One patient, who has been in the hospital for four of the past five months, noted marked jitteriness and tachycardia on 50 to 80 mg. a day in divided dosage along with small inhalations p.r.n. When the oral drug was discontinued, his nervousness and tachycardia disappeared but he had to use the nebulizer more often to control his daily wheezing. In most cases the results are equivocal and it is impossible to evaluate them correctly at the time of this report. One hospital case was treated solely on oral medication of 80 to 120 mg. daily for a week

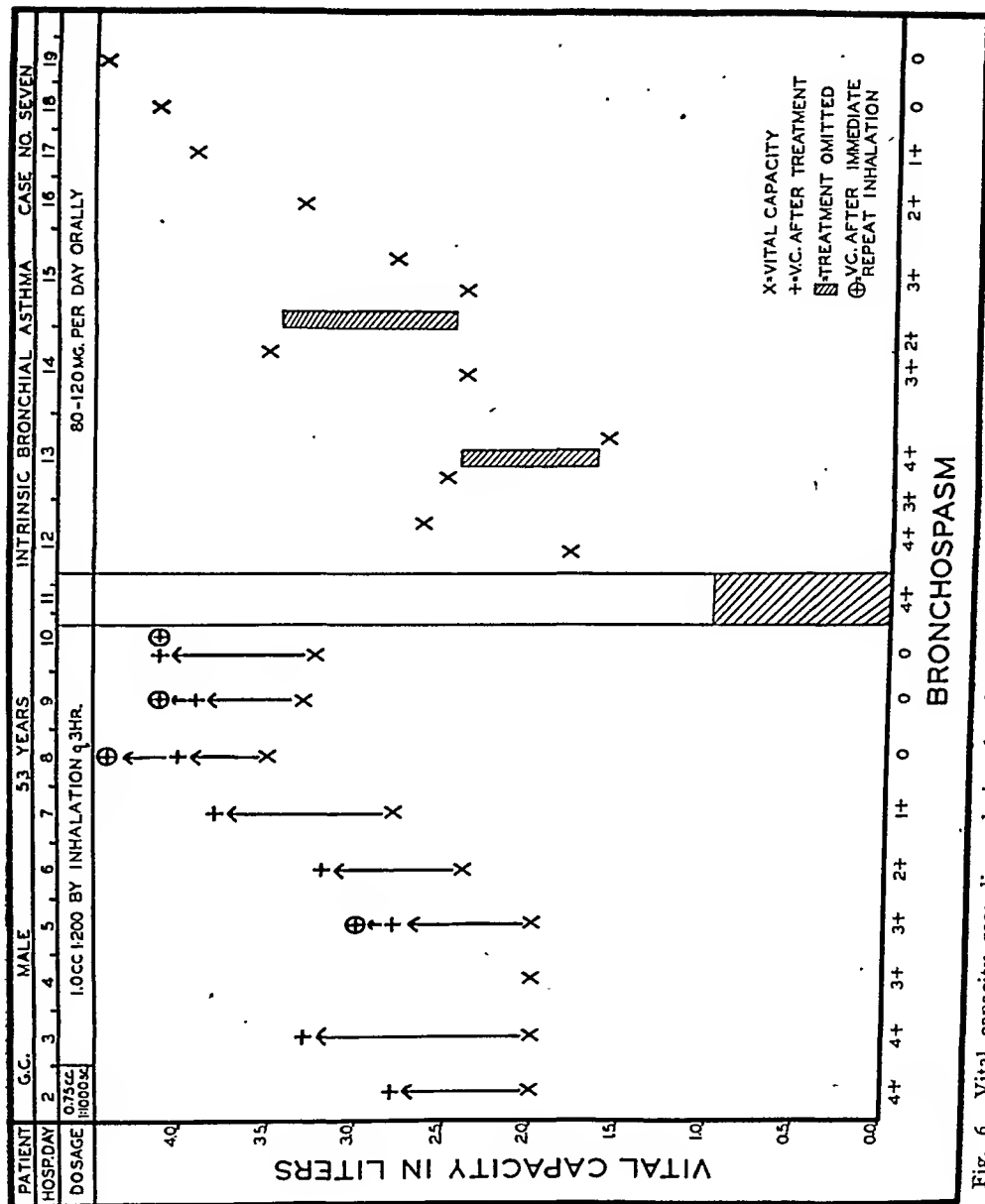


Fig. 6. Vital capacity recordings during hospital course (Case 7) treated with isuprel by various routes.

(Fig. 6). He had an excellent course but complained of persistent nervousness.

It might be said now that oral isuprel may have a place in the manage-

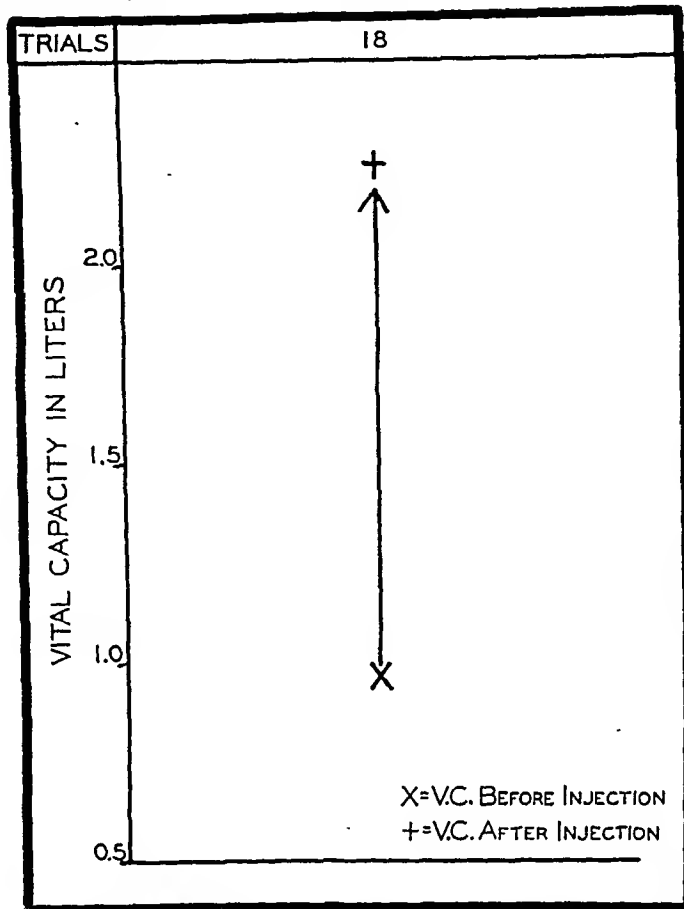


Fig. 7. Average of eighteen vital capacity recordings on fifteen hospital patients with moderate to severe bronchospasm using 0.25 c.c.-0.75 c.c., 1:1,000 isuprel subcutaneously.

ment of the chronic asthmatic who wheezes some every day but rarely has a severe attack. Its action appears to be too slow to warrant its use in the acute stage of asthma.

#### EFFECT ON BLOOD PRESSURE AND PULSE

The response of the blood pressure depends greatly on the amount of bronchospasm present. Osgood<sup>12,13</sup> in his discussion of the blood pressure fluctuations in bronchial asthma, has pointed out that such fluctuations are a constant finding, that their excursions depend upon the severity of the attack and that they signify the amount of respiratory obstruction present. The increased negative intrathoracic pressure during the forced and difficult inspiration period leads to a pooling of blood in the lungs and makes the filling of the left heart more difficult. This represents the low point in the fluctuations. Conversely, on expiration more blood is



sent to the left heart; therefore the systolic pressure is greater and the high point of the fluctuation occurs in this phase of the respiratory cycle. Since this fluctuation is an indirect measure of respiratory obstruction, its abolition may be considered an indication that less obstruction exists. Isuprel effectively abolished or markedly decreased this fluctuation and did so in an especially dramatic fashion when the bronchospasm was greatest. The results varied generally with the amount of bronchospasm present. When the spasm was 3+ to 4+ a marked drop towards normal levels was noted in both pressure phases. If the spasm was minimal, a moderate rise in the systolic reading and a corresponding fall in the diastolic was seen, a widened pulse pressure resulting.

Six studies of the blood pressure and pulse changes in five normal individuals were done. Three of the studies accompanied the 1:200 dilution by oxygen-aerosolization and three were carried out with the subcutaneous injection of 0.33 c.c. of the 1:1,000 dilution. The systolic pressure showed an average increase of 13 mm. of mercury with the inhalatory route and 22 millimeters with the subcutaneous route. The pulse pressure showed an average increase of 16 mm. of mercury with inhalation and 39 mm. with subcutaneous injection. The pulse increased an average of 18 and 50 beats per minute with the inhalatory and subcutaneous routes, respectively. This compares with Blumgart's studies<sup>6</sup> in ten normal subjects to whom 0.5 to 1.0 c.c. of 1:1,000 solution of epinephrine was given subcutaneously. He found an average rise in the systolic pressure of 38 mm. of mercury, an average increase in pulse pressure of 48 mm. of mercury and an average increase in the pulse rate of 16 beats per minute.

Isuprel, by the inhalatory route, caused minimal side reactions which disappeared quickly in the normal subjects. However, the subcutaneous injections in the normals led to marked palpitations, pounding, fullness in the chest and moderate headache. These symptoms began within two minutes and persisted to a disturbing degree for approximately one-half hour. The basal blood pressure and pulse levels were re-established shortly thereafter. The complaints of the patients following equal or larger amounts by subcutaneous injection were fewer than with the normals. Apparently the relief of their dyspnea was so outstanding as to cause less consciousness of the cardiovascular side effects which were paramount in the observations of the normal subjects.

A total of 118 recordings was made of the blood pressure and pulse changes accompanying oxygen-aerosolization and subcutaneous injections in the first twenty-nine hospitalized patients. Eighty-six recordings were made when various dilutions of isuprel were aerosolized by oxygen for varying degrees of bronchospasm. Thirty-two recordings were taken of the changes accompanying subcutaneous injection (Fig. 8.) The average widening of the pulse pressure in the 118 trials was only seven millimeters of mercury. In the thirty-two subcutaneous trials the pulse pressure increased by 10 mm. of mercury, while in the eighty-six oxygen-aerosolization record-

ings the increase was only 6 millimeters. The increase in pulse pressure in the asthmatics in this study is due almost entirely to a lowering of the diastolic phase. A peripheral vasodilation of the finer arterioles therefore

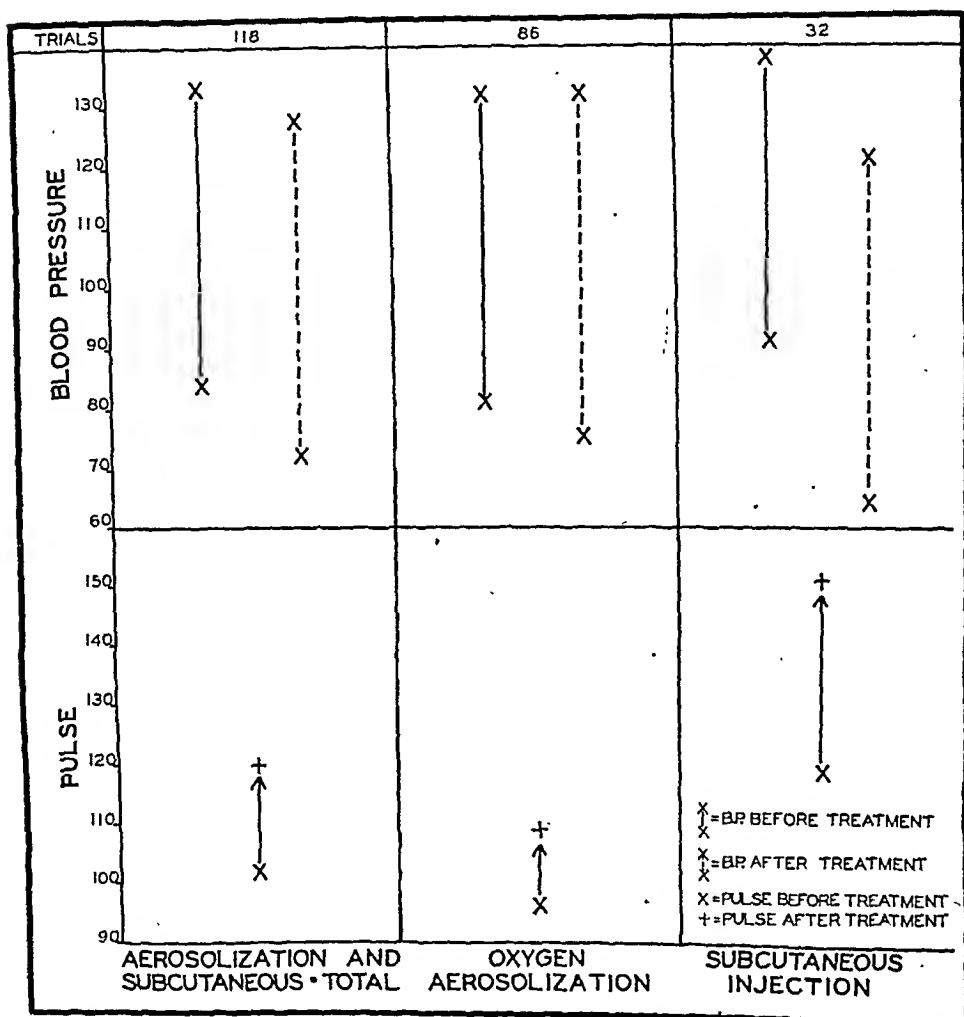


Fig. 8. Averages of 118 recordings of the blood pressure and pulse changes occurring with various dilutions of isuprel by oxygen-aerosolization and subcutaneous injection in twenty-nine hospital patients.

probably occurs, implying an excess of the sympathin I fraction. The pressor action observed with epinephrine, which is due to a predominance of sympathin E and is especially disturbing to hypertensives, appears to be present to a lesser degree with isuprel.

The average increase in pulse in the total group is from 102 to 120 beats per minute. Considered separately, the subcutaneous route caused a jump in the pulse rate from 119 to 151, an increase of 32 beats per minute, while the oxygen-aerosol route showed a lesser change from 96 to 109, an increase of 13 beats per minute (Fig. 8).

The differences in blood pressure and pulse changes (Fig. 8) between

the oxygen-aerosolization and subcutaneous routes are due to the fact that the inhalatory group represents a mixture of all degrees of bronchospasm from 1+ to 4+, while all the patients receiving the subcutaneous isuprel were in 3+ to 4+ bronchospasm. For all practical purposes, the results noted with subcutaneous injections are also seen where extreme bronchospasm is treated by oxygen-aerosolization. Observations on the eleven patients treated since the original report are in conformity with the above as regards the blood pressure and pulse changes.

#### SIDE REACTIONS

Table I illustrates the general type and frequency of side reactions noted in (1) 187 individual oxygen-aerosolization trials on eighty-two ambulatory patients and (2) more lengthy observations over a period of days in the first twenty-nine hospitalized patients treated by both the oxygen-aerosol and the subcutaneous routes. The inhalatory route is generally very benign as far as undesirable side reactions are concerned. The majority of the ambulatory patients had either no reactions or slight jitteriness or palpitations which wore off quickly. The oxygen-aerosol route in the hospital cases showed essentially the same benignity and not one patient felt that these reactions detracted from the relief of his dyspnea. More serious reactions—marked palpitations being the most outstanding—were seen from the subcutaneous route, especially if the 1:1,000 dilution was used in doses of 0.5 c.c. or more. Five patients also showed nausea and vomiting but three had these symptoms before the treatment. In general, 0.20 c.c. to 0.33 c.c. of 1:1,000 produced the best relief of dyspnea with minimal side effects. Seven patients were given frequent subcutaneous injections with no cumulative effect noted. Very few of the undesirable side reactions persisted for more than five to fifteen minutes. As noted above, the smaller dilutions by injection caused fewer side effects but were less effective in aborting dyspnea.

Only a few observations can be made in this report regarding ill effects of oral isuprel. Attendant nervousness and tachycardia have been observed with doses above 50 mg. daily. These symptoms wore off quickly when the drug was omitted and did not reappear with the smaller doses.

#### CONCLUSIONS

1. Isuprel (1-(3, 4'-Dihydroxyphenyl)-2-isopropylaminoethanol), a new pneumodilator drug, appeared to be effective in relieving the dyspnea of bronchial asthma.

2. Three routes of administration were employed: oxygen-aerosolization, with doses of 1.0 c.c. of 1:100 dilution every three hours; subcutaneous, with doses of 0.20 to 0.33 c.c. of 1:1,000; and oral with doses of 30 to 60 mg. daily. These dosages were generally the most effective in their respective routes of administration.

3. Results are presented of 187 trials in eighty-two ambulatory patients

treated by oxygen-aerosolization and in forty hospitalized patients treated by one route alone or by a combination of routes.

4. Subjective relief from bronchospasm was observed and correlated with improvement in the vital capacities. The greater the degree of bron-

TABLE I. SIDE REACTIONS

Reaction	Ambulatory Patients	Hospital Patients		
	Oxygen Aerosol	Oxygen Aerosol	Subcutaneous	
			0.5-0.75 cc.	0.25 0.33 cc.
None	149	8	..	..
Palpitation				
Slight	10	8	1	4
Moderate	4	4	1	3
Marked	2	1	6	1
Dizziness				
Slight	..	1	3	1
Moderate	..	1	1	1
Marked	..	..	1	..
Jittery				
Slight	7	3	1	..
Moderate	2	..	..	..
Marked	5	..	1	..
Headache or Throbbing	2	2	1	1
Euphoria	1	..	..	..
Nausea	..	1	4	1
Vomiting or Retching	..	..	5	1
Epigastric Pain	..	..	1	..
Sweating	1	..	1	..
Flush	..	..	..	1
Precordial Pain	..	..	1	..
"Filled Up"	..	2	..	..
Dryness of Mouth	4	..	..	..
Sore Tongue or Mouth	..	2	..	..
Tingling of Lips	..	..	1	..
Pink Sputum	..	2	..	..

chospasm, the greater was the improvement in vital capacity. This improvement was also observed in patients with coughing paroxysms who were free of bronchospasm.

5. The fluctuations in blood pressure observed in asthmatics, namely, the variation in the systolic and diastolic readings in inspiration and expiration, were effectively abolished or markedly decreased and in an especially dramatic fashion when the bronchospasm was greatest.

6. Undesirable pressor effects and tachycardia were minimal and in general corresponded to the individual's tolerance to sympathomimetic amines. Reactions may be alarming if more than 0.5 c.c. of 1:1,000 is given

subcutaneously. The drug should not be used intravenously. Sensitive patients should get inhalatory doses of 0.5 c.c. of the 1:200 dilution and subcutaneous doses of 0.1 c.c. of the 1:1,000 dilution. These doses may be gradually increased to determine individual tolerance.

7. The epinephrine-fast state observed in eleven patients responded favorably. No fastness to isuprel was observed.

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## NORTHWEST POLLENS

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IN considering pollens of the Northwest, one is confronted with the flora of two distinct climates. If one checks the charts in most of the books on allergy, including the *Manual of Allergy Laboratory and Diagnostic Procedures*, as put out by the American College of Allergists, he finds the plants under one heading for northern California, northern Nevada, the whole state of Oregon and the whole state of Washington. Vaughan<sup>3</sup> considers western Washington, western Oregon and northern California separately, and the floras of each area are found to be entirely different; although the pollinating dates are inaccurate for the Washington area, it does give a truer picture.

If one looks at the topography of the northwestern states and considers the source of their weather, he immediately sees the reason for such a marked difference of climate and flora within a few miles. The Cascade range of mountains roughly parallels the coast 100 miles inland, and is the true dividing line (Fig. 1). This range is very high, with such peaks as Mount Baker, Mount Rainier, Mount Hood and Mount Shasta, with elevations up to 14,408 feet. During the months of January and February, there is a prevailing southeast wind, but the storms actually come from the southwest, which would bring them from over warm ocean currents. Thus, as this warm moist ocean air nears the high cold Cascades, there is condensation and, therefore, marked rainfall. Seattle, which is eighty-five miles inland, has an average rainfall of 33.28 inches, and Wenatchee, which is just thirty miles east of the divide, has 8.75 inches of rainfall. In Oregon, Portland, approximately sixty miles from the coast, has an annual rainfall of 41.62 inches; Eugene, fifty miles inland, has 37.83 inches; and Bend, just twenty-five miles east of the divide, has 12.72 inches of annual rainfall.

One would expect cold winter months at this latitude, but heavy frosts are not common even as far north as Juneau, Alaska. During March, April, May and June, the winds are generally from the south with less moisture, and there is considerable warm weather which is conducive to rapid plant growth. However, at the height of the summer season, July, August and September, the winds shift, coming from the north, off the Bering Sea area and the North Pacific, tempering the summer climate. This type of season, it is thought, is not conducive to maturing the usual fall weeds in this area. In October, November and December the air currents again come from the southwest but, due to the fact that they travel circularly, counterclockwise, the prevailing winds again are from the southeast. For these reasons, the 100-mile-inland coastal strip of Oregon and Washington has a very mild winter and moderately warm

Lecture presented March 6, 1946, American College of Allergists, Regional Spring Instructional Course, University of Oregon Medical School, Portland, Oregon.

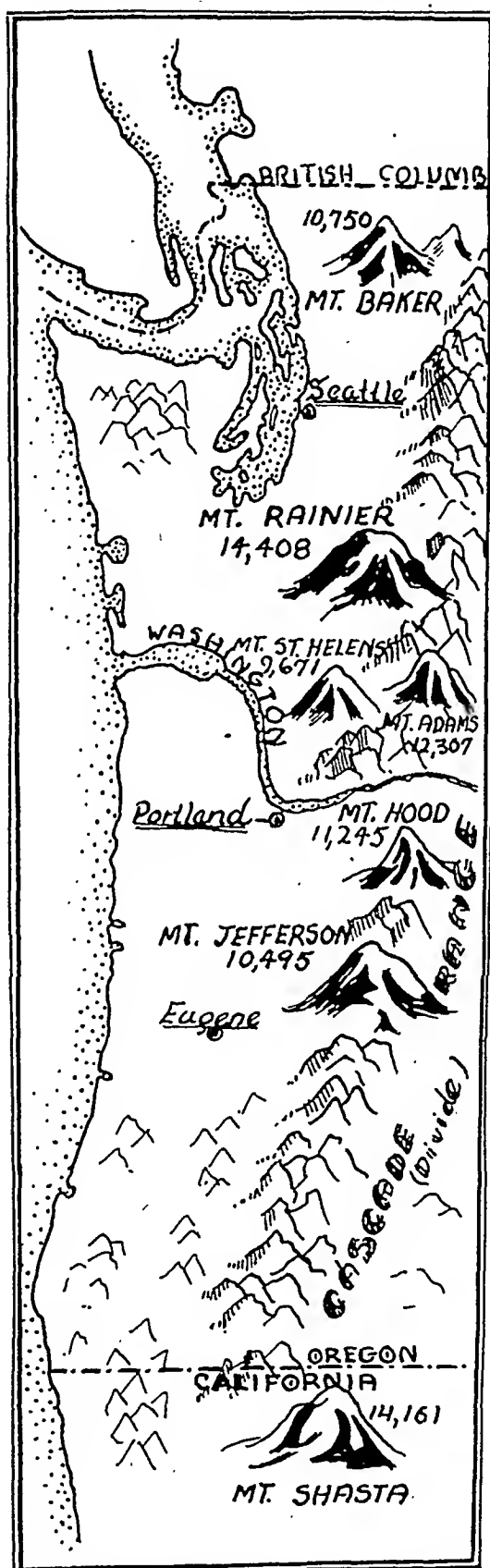


Fig. 1. Topography of Pacific Northwest area.

# NORTHWEST POLLENS—STROH

summer. In the areas east of the Cascade range, the climate is mid-western in nature, with hot dry summers and cold snowy winters. The fall season is again ideal for weed growth; short ragweed (*Ambrosia*

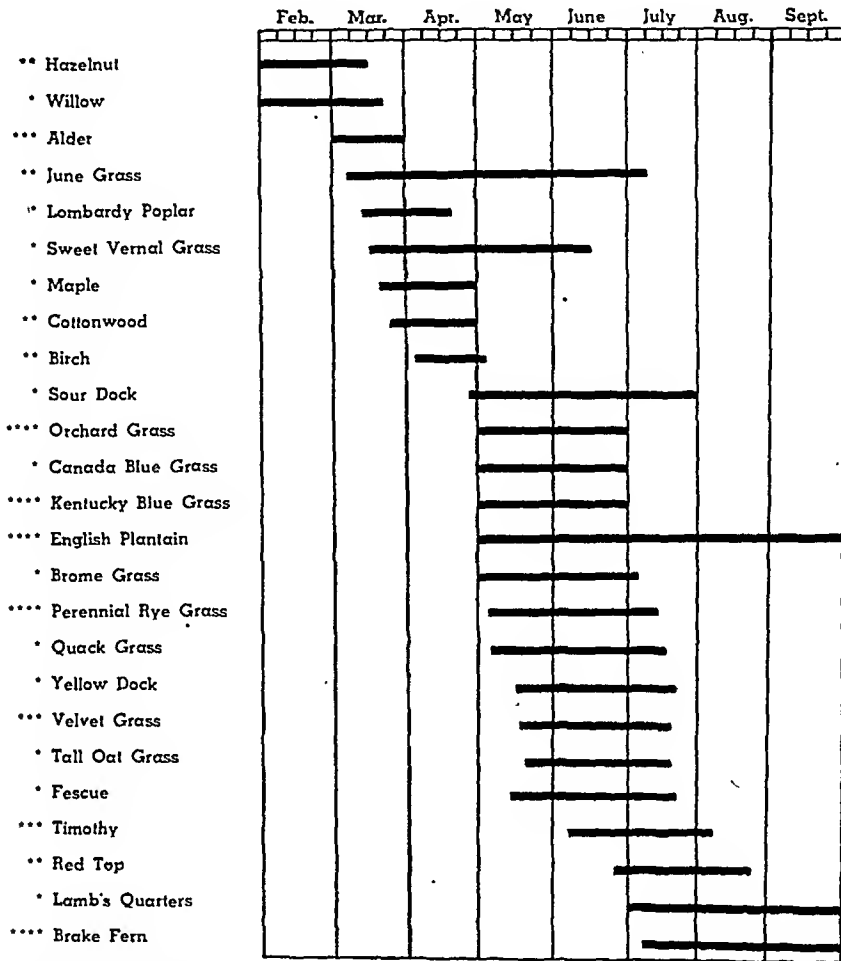


Fig. 2. Pollinating dates of hay fever plants in Seattle. Asterisks indicate relative pollen concentration.

*elator*), western ragweed (*A. psilostachya*), giant ragweed (*A. trifida*), desert sagebrush (*Artemisia tridentata*) and Russian thistle (*Salsola pestifer*) are present.

In speaking of Northwest pollens, allergists who practice along the coast think chiefly in terms of pollens within the coastal area, which would hold from northern California to Juneau, Alaska. They think of the pollens east of the Cascade range as midwestern. I will include some of the important offenders east of the Cascades.

The Seattle pollen season begins about the first of February (Fig. 2) with willow (*Salix scoleriana*) and hazelnut (*Corylus californica*). *Salix lasiandra* and *S. sitchensis* are not prevalent. Due to the facts that willow pollen is partly insect-borne and that rains are prevalent during their



anthesis, it cannot become a serious offender in the northwest area. South of Portland, there are large groves of hazelnuts. The one most commonly grown is *Corylus avellana*, occurring in its several varieties.

## TREE POLLEN SEASON—1941

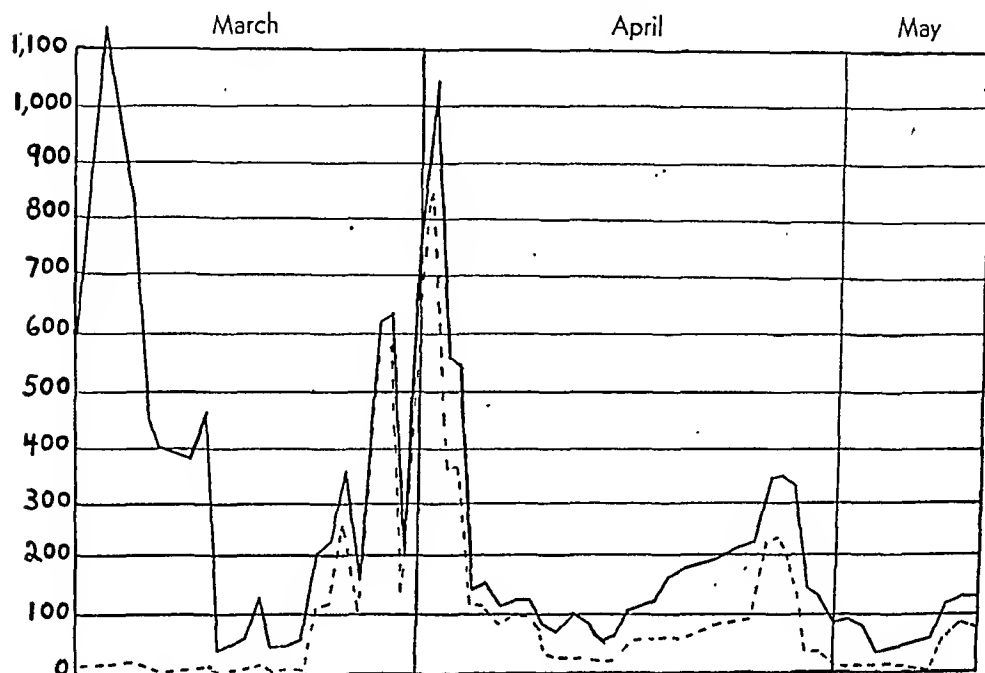


Fig. 3. Pollen grains per unit slide area (1.8 sq. cm.). Dotted line represents the pine season.

White aveline, Barcelona, Daviana, and Du Chilly are others. The pollinating dates vary according to the variety, extending over a period of about ten weeks. In this area, spring hay fever is definitely increasing, proving the potency of tree pollen when present in large quantities. In this same area, black walnut (*Juglans nigra*) and English walnut (*J. regia*), which can be offenders, pollinate from late March through April.

Alder (*Alnus oregona*) starts pollinating about March 1, reaching a peak sometime between March 10 and 20. This peak is one of the highest of any season and may reach a count of 1,000 or more per 1.8 sq. cm. per day (Fig. 3). It is not unusual in the spring to find patients sensitive only to alder pollen, and status asthmaticus is not uncommon at this time of the year. Elm (*Ulmus americana*) and the Lombardy poplar (*Populus nigra*), an introduced species, are not very common. The maples (*Acer macrophyllum* and *A. rubrum*) are partly insect-pollinated and probably not important. The cottonwood (*Populus trichocarpa*) does not pollinate over a long enough period of time to be a serious offender. The aspen (*P. tremuloides*) is relatively scarce. These pollinate in late March. In the early part of April, birch (*Betula pendula*) pollinates and is next in importance to alder among the trees.

## NORTHWEST POLLENS—STROH

(*B. fontinalis*) is more common in eastern Washington. Sycamore (*Platanus acerifolia*) appears only in scattered areas throughout the cities, and the ash (*Fraxinus oregona*) is not common. Box elder (*Acer*

### GRASS POLLEN SEASONS—1940, 1941

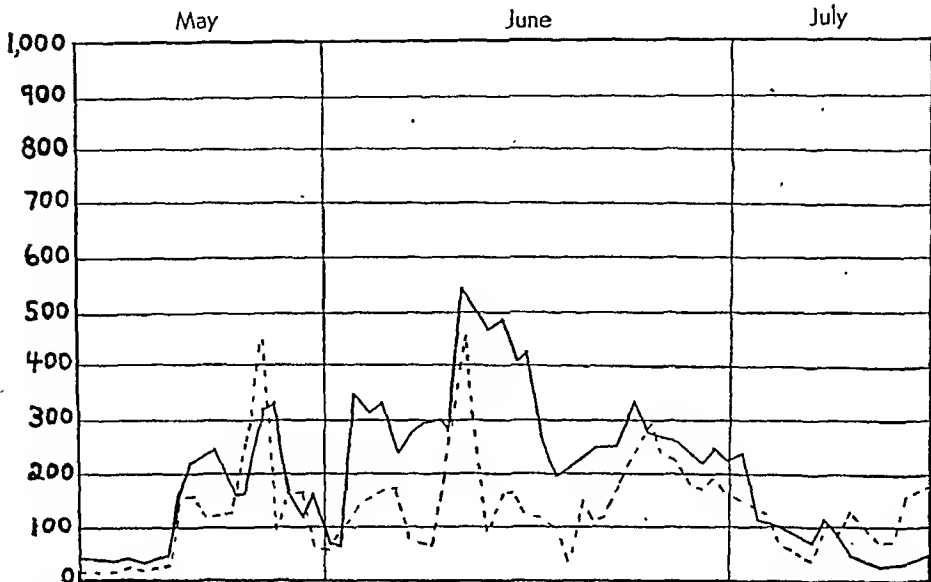


Fig. 4. Pollen grains per unit slide area (1.8 sq. cm.). Solid line is for 1940, and dotted line is for 1941.

*negundo*) and locust (*Robinia pseudoacacia*) are sparingly present in the area east of the mountains. Oak (*Quercus garryana*) appears scattered over the flat lands throughout the northwest and is a factor where abundant. Numerous, introduced, ornamental trees and shrubs, such as dogwood (*Cornus nuttallii*), common Indian plum (*Osmaronia cerasiformis*), mountain ash (*Sorbus americana*) and red flowering currant (*Ribes sanguineum*), are of doubtful importance, if ever a factor. A large variety of conifers grow in this district, but they do not seem to contain an excitant factor. In the eastern part of the state yellow pine (*Pinus ponderosa*) has been reported to be a factor.<sup>1</sup> However, Seattle pine pollen counts during the season of 1941 rose to 1,000 per 1.8 sq. cm. (Fig. 3), and many newspaper articles appeared telling of the clouds of yellow pollen and "sulphur" streams; even the birds of the forest were yellow with pollen. Scouring rush (*Equisetum telmateia*) sporulates heavily in certain coastal areas from March to May. It is a menacing weed and its spores appear frequently on the slides, but I have never found it to be a factor in hay fever.

The grass season starts moderately about April 1, with low speargrass (*Poa annua*) and sweet vernal grass (*Anthoxanthum odoratum*). The latter is distinguished by its pleasant, sweet odor. The season becomes in-

tensified about May 15, 'reaching its height during the early part of June and declines by July 15 (Fig. 4). Many grasses pollinate in small quantities until October. Canada blue grass (*P. compressa*) and Kentucky blue grass (*P. pratensis*) start about May 1. The latter is one of the widely distributed grasses in this area and a major offender. English plantain (*Plantago lanceolata*) starts as early as May. Like other weeds, it is not found to be allergenic as often as the grasses, but is potent and can be the only offender in some cases during July and August. Greater plantain (*P. major*) is rather scarce. Quack or wheat grass (*Agropyron repens*), perennial rye (*Lolium perenne*) and Italian rye (*L. multiflorum*) also flower at this time. The other ryes, such as *Elymus hirsutus*, *E. glaucus*, *E. mollis*, and *E. canadensis*, are less abundant but will likely become more important in the future. *Bromus sterilis*, *B. mollis*, *B. marginatus*, *B. carinatus*, *B. ciliatus* and *B. racemosus*, are fairly common and are increasing in abundance. Orchard grass (*Dactylis glomerata*) is widely distributed and bears one of this area's most potent pollens. Tall oat grass (*Arrhenatherum elatius*) appears as large plumes along the graded roadsides and is increasing in abundance. Velvet grass (*Holcus lanatus*) is rather a showy grass with silvery colored leaves, and is one of the chief offenders. Smooth velvet (*H. mollis*) is sparsely distributed. Timothy (*Phleum pratense*) and most of the fescues (*Festuca*) start pollinating about July 1. There are many of the latter (some without common names), namely, *F. myuros*, rat's-tail fescue; *F. subulata*, bearded, fescue; *F. octoflora*, six-weeks fescue; *F. dertonensis*; *F. elatior*, meadow fescue; *F. ovina*, sheep fescue; and *F. rubra*, red fescue. *F. elatior* and *F. dertonensis* are probably the most important of this group. The barleys, *Hordeum murinum*, *H. jubatum* and *H. nodosum* are flowering at this time, but the quantity of pollen that they shed is so small that they cannot be considered important. Crested dogtail (*Cynosurus cristatus*) and Koeler's grass, or June grass, (*Koeleria cristata*) are on the increase and, no doubt, will become more important. Red top (*Agrostis alba*) and bent grasses (*A. maritima* and *A. tenuis*) start pollinating during the later part of June. It is not unusual to see a field that was silvery in color from velvet grass become a brownish red a few weeks later due to red top, giving the impression that the former grass has dried and gone to seed. Other minor grasses belonging to this genus are the creeping bent (*A. palustris*), water bent (*A. verticellata*) and spike red top (*A. exarata*). Other grasses, of little or no importance, are slender hair grass (*Deschampsia elongata*), tufted hair grass (*D. caespitosa*), annual hair grass (*D. danthonioides*), rabbits' foot grass (*Polypogon monspeliensis*), rice cut grass (*Leersia oryzoides*), silver hair grass (*Aira caryophyllea*), and crab grass (*Digitaria sanguinalis*), which looks like the common Bermuda grass of the South.

Grama, Bermuda and Johnson grasses do not grow in the Northwest. The weed, barnyard grass (*Echinochloa crusgalli*), is fairly abundant in some areas east of the Cascades.

The weed pollen season for the coast is of minor importance as compared to the other seasons. Yellow dock (*Rumex crispus*), bitter dock (*R. obtusifolius*) and sheep sorrel (*R. acetosella*) have a wide distribution but are not abundant. These three pollinate together with the grasses in May and June, but I get few allergic reactions to them in testing.<sup>2</sup> Lamb's quarters (*Chenopodium album*), pigweed (*Amaranthus retroflexus*) and mugworts (*Artemisia vulgaris* and *A. heterophylla*) gave strongly positive reactions at times and must be considered. Burweed marsh-elder (*Iva xanthifolia*), nettle (*Urtica lyalli*), and cockle bur (*xanthium*) grow here, but rarely do I get positive reactions from their pollen.

The commonest weed east of the Cascades is Russian thistle (*Salsola pestifer*), which pollinates from mid-June to mid-September. In eastern Oregon, sagebrush (*Artemisia tridentata*) is the commonest in some areas. Mountain sage and prairie sage are seldom found. Western water hemp (*Acnida tamariscina*) and Marsh elder (*Iva xanthifolia*) are factors in some areas. Mugwort (*Artemisia vulgaris*) and wormwoods, usually *A. vulgaris* and *A. heterophylla*, also salt bush (*Atriplex truncata*), are found occasionally. These are factors in hay fever, and pollinate from mid-June to late fall. Western ragweed (*Ambrosia psilostachya*) and false ragweed (*Franseria acanthicarpa*) are found, as is a little short ragweed (*Ambrosia elatior*). These are increasing in abundance east of the Cascades, but do not compare in importance with Russian thistle and sagebrush.

The ferns shed an abundance of spores in August and are found growing everywhere in the Puget Sound area. The total spore count almost equals that of the grasses.<sup>2</sup> However, I can say that I have never seen a true case of fern-spore hay fever. The common brake, or bracken (*Pteridium aquilinum*) produces over 90 per cent of the spores found. The spores of this and the sword fern (*Polystichum munitum*) are easily distinguished from the pollen grains on the slides. Other species are not common.

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I wish to express my indebtedness to Dr. G. N. Jones, formerly in charge of the University of Washington Herbarium, for the identification of numerous plants; to Dr. C. Leo Hitchcock, of the University of Washington and to Dr. Helen M. Gilkey of the Oregon State College, for their information on plant distribution and pollinating dates.

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A limited number of the comprehensive abstracts of the lectures, which were presented at the Fall Graduate Instructional Course in Philadelphia in November, 1946, are available at \$6 per set. Each set is composed of forty-three printed lectures, which are perforated for a standard ring book and thus form an up-to-date manual of allergy, with complete bibliography.

# SKIN TESTING WITH FRACTIONS OF CHOCOLATE

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Brooklyn, New York

CHOCOLATE is one of the most common food offenders among allergic individuals. Nevertheless the incidence of positive skin reactions to chocolate is not very large. Moderate or marked skin reactions with this allergen are not common. Clinically however, many allergists and pediatricians eliminate chocolate routinely from the diets of their allergic patients and note some degree of improvement in many of them.

This study was undertaken to determine whether the skin reactions would vary if the skin were tested with extracts of the different parts of the cocoa bean and with extracts of the various finished chocolate and cocoa products.

Chocolate is derived from the cocoa bean. The bean is roasted first and then crushed. The resulting product is known as cocoa nibs. The shells are separated from the cocoa nibs by a rotating process. Better grades of chocolate are practically free of shell. Shells are considered as adulterants and are used as cattle feed. The nibs are ground and milled thoroughly to a thin paste which on cooling forms a hard cake. This is known as cocoa liquor or plain chocolate. By extracting 50 per cent or more cocoa butter from the liquor, press cakes result. These are pulverized to give cocoa powder.

TABLE I. COMPOSITION OF CHOCOLATE

Type	Per Cent Chocolate Liquor	Per Cent Sugar	Per Cent Total Fat	Per Cent Whole Milk Solids
Bitter	100	0	50-56	0
Bittersweet	80-95	5-20	40-50	0
Darksweet	25-45	40-50	34-42	0
Lightsweet	5-15	55-68	31-39	0
Sweetmilk	7-17	35-55	28-39	12-20

There are many types of chocolate available on the market. There is bitter chocolate which is pure chocolate without the addition of sugar or other ingredients, and this is commonly called chocolate liquor. This chocolate liquor is used as a base for the manufacture of sweet and milk chocolate by the addition of sugar, milk, flavors and other ingredients. To make the chocolate fluid, various amounts of cocoa butter are added to the mixture.

The composition of chocolate varies in its content of chocolate liquor, sugar and other ingredients in the mixture. The approximate compositions of common types of chocolate are given in Table I.

From the Allergy Clinic of the Beth Moses Hospital.  
The various chocolate products were supplied through the courtesy of Rockwood Chocolate Company of Brooklyn.

# SKIN TESTING WITH CHOCOLATE—ZOHN

## TABLE II. INTRACUTANEOUS TESTS

	Clinically Chocolate Sensitive	Cocoa Bean	Cocoa Shell	Cocoa Nib	Cocoa Liquor	Cocoa Powder	Control Saline
1 R L	+	0	0+	0	0+	0	0
2 N Z	+	SI	SI+	0	0	0+	0
3 B L	0	0	0	0	0	0	0
4 F F	+	SI—	SI	0+	0	SI—	0
5 Y S	0	SI—	SI—	SI—	SI	SI—	0
6 Y T	0	SI	SI	SI—	SI—	SI—	0
7 R P	0	0	0	0	0	0	0
8 H H	0	SI	SI	0	0	0	0
9 R G	0	0	0	0	0	0	0
10 M C	+	0+	0	0	0	0	0
11 J S	+	0+	0	0	0+	0	0
12 M L	+	SI—	SI+	SI—	SI	SI	SI—
13 M S	+	0	0+	0	0	0	0
14 Y S	+	SI	SI—	0	0	0	0
15 W W	+	SI—	SI—	SI—	SI—	0+	0+
16 E G	0	0	0	0	0	0	0
17 D B	+	SI	MKD	SI—	0	0	0
18 N D	0	SI	SI+	SI—	0	0	0
19 K	0	0	SI	0	0	0	0
20 B S	+	SI—	SI—	0	0	0	0
21 R G	+	SI++	SI+	SI	SI+	SI—	0
22 S H	+	SI	SI—	0+	0	0	0
23 R C	0	0	0	0	0	0	0
24 J P	+	0	0	0	0	0	0
25 R L	+	0	0	0	0	0	0
26 K G	+	SI—	0	0	0	0	0
27 N P	+	0	0	0	0	0	0
28 I K	0	SI—	0	SI—	0	0	0
29 O R	+	0	0	0	0	0+	0
30 Z K	+	0	0+	0	0	0	0
Summary: Skin Reactions:							
Slight Minus		7	5	7	2	4	1
Slight		7	4	1	2	1	0
Slight Plus		1	4	0	1	0	0
Mod. to Marked		0	1	0	0	0	0
Totals		15	14	8	5	5	1

O=Negative reaction

SI—=More than negative, less than slight

SL=Slight positive reaction

SL+=More than slight positive, less than moderate

Chemically, chocolate consists of cocoa butter, sugar, moisture and cocoa solids. The cocoa solids consist of:—

crude fiber	organic mineral constituents
ash	phosphorous pentoxide
cocoa starch	silica
other digestible carb.	lime
caffeine	magnesium oxide
theobromine	potash
nitrogen	soda
protein	ferric oxide
	alumina
manganese	tartaric acid
copper	acetic acid
chlorides	citric acid
sulphates	oxalic acid
cocoa tannin	
pectin	
cocoa red	

In order to determine whether the skin reaction varied when different parts of the bean were used for testing, extracts were made with cocoa

# SKIN TESTING WITH CHOCOLATE—ZOHNN

TABLE III. PASSIVE TRANSFER STUDIES WITH FOUR SUBJECTS

	Subject Sensitized	Subject Tested	Cocoa Bean	Cocoa Shell	Cocoa Nib	Cocoa Liquor	Cocoa Powder
S. Serum	11/6/44	11/9/44	Sl-mod	Mod	Sl	Sl-mod	Sl
G. Serum	11/6/44	11/9/44	0	0	0	0	0
N. Serum	10/30/44	11/3/44	Sl+	Sl+	Sl	Sl+	Sl—
R. Serum	10/30/44	11/3/44	Sl—	Sl—	Sl—	0	Sl

bean, shells, nibs, liquor and powder. Extracts were prepared in the usual manner. They were ground, defatted first with toluol and then washed four times with water-free ether. To the dried defatted powder, buffered saline was added and covered with toluol. After seven days the extract was filtered.

Thirty atopic cases were tested with these extracts by the intracutaneous method using 0.1 mg. concentration. There were nineteen cases with positive clinical history of chocolate sensitivity and eleven with negative histories (Table II).

The skin reactions in this series were predominantly slight-minus to slight. Occasionally a slight-plus and in one instance a marked reaction was obtained. Cocoa bean and cocoa shell gave the greatest number of positive reactions. There was no definite correlation between clinical symptoms and positive skin reactions.

Four cases were selected with marked clinical histories of chocolate sensitivity. These cases developed allergic symptoms within one-half to two hours after ingestion of chocolate. Serum was obtained from these individuals and passive transfer studies were made using same extracts as in Table II. In one case we failed to get any positive reaction in spite of the positive clinical history. The other three cases gave slight to moderate reactions (Table III).

Since there was no marked difference observed in testing with the various parts of the cocoa bean, we thought it advisable to perform skin tests with various chocolate and cocoa products sold to the consumer. The following extracts were thus prepared:

1. Natural Breakfast Cocoa No. 5—natural cocoa powder prepared by extracting cocoa butter. This contains about 22 per cent butter fat.

2. Natural Solvent Extracted Cocoa Powder No. 6—low fat—contains about 0.20 per cent total fat.

3. Semi-sweet chocolate, dark No. 8—prepared by blending sucrose, chocolate liquor, flavor and sufficient cocoa butter to make it fluid. It contains about 33 per cent cocoa butter and vegetable lecithin.

4. Light-sweet chocolate coating No. 9—contains about 32 per cent cocoa butter and 64 per cent sugar.

5. Natural chocolate liquor No. 10—contains between 52 to 56 per cent cocoa butter.

6. Sweet milk chocolate. No. 12—low in chocolate liquor, high in total fats and moderately high in dry whole milk constituents.

# SKIN TESTING WITH CHOCOLATE—ZOHN

TABLE IV. TESTS WITH EXTRACTS OF CHOCOLATE PRODUCTS

Name	Clinical Positive	Natural Breakfast Cocoa No. 5	Natural Solvent Extracted Cocoa No. 5	Semi-Sweet Chocolate No. 8	Light Sweet Chocolate Coating No. 9	Natural Chocolate Liquor No. 10	Sweet Milk Chocolate No. 12
1 R G	+	0	0	0++	0++	0++	0++
2 M O	0	0	0	0	0	0	0
3 E N	+	0	0	0	0	0	0
4 E S	+	0	0+	0	0	0	0
5 M J	+	0+	0++	SI	0+	0++	0+
6 B Z	0	0	0+	0	0	0	0
7 L M	0	0	0+	SI—	0	0+	0+
8 B W	+	0++	0+	0++	0++	0+	0++
9 C M	+	SI	0++	0	0	0++	0++
10 A F	+	0	0	0	0	0	0
11 A A	+	SI	SI	SI+	SI	SI	SI—
12 J K	+	0	0	0++	0+	0	0+
13 A L	0	0	0+	0	0	0	0
14 S L	0	0	0	0+	0	0	SI
15 T W	+	0	0	0	0	0	0
16 I H	0	0	0	0	0	0	0+
17 P L	0	0	0+	0	SI	0	0++
18 L W	+	0+	0	0++	0	0	0++
19 E M	+	0	0+	0	0	0+	0
20 J L	+	0++	SI+	0++	0++	0	0
21 L G	+	0	0+	0	0	0+	0
22 H K	0	0	0	SI—	0	0	SI+
23 H F	0	0	0	0	0	0	0
24 K L	+	0	0	0	0	0	SI
25 M K	0	0	SI	SI	SI	SI+	SI—

0 =absolutely negative

0+ =slightly more than negative

0++ =a degree more than 0+

SI— =a little less than slight

SI =slight

SI+ =more than slight

Twenty-five allergic individuals were tested with extracts of the finished chocolate products commonly used. The skin reactions were negative to slight and did not show any variations, regardless of the type of extract used (Table IV). There were fifteen patients in this series who were chocolate sensitive clinically, and ten were negative.

## DISCUSSION

An attempt has been made to ascertain why a substance like chocolate which is a common food in our daily diet produces allergic manifestations so frequently and yet on skin tests fails to give positive skin reactions in a great many instances and rarely more than a slight reaction in most cases. Many allergists routinely remove chocolate from the diet of their allergic patients regardless of the results of the skin tests and note definite improvement in their patients. There is no standard method of preparing chocolate extracts today. Cocoa bean and various chocolate bars are used by allergy clinics in the preparation of their antigen. It was thought advisable to assay the various types of chocolate extracts using different parts of the cocoa bean and also finished chocolate products commonly ingested by the individual patient and to determine which extract is most suitable for skin testing. From the viewpoint of skin tests, it seems best to use the cocoa bean in the preparation of the chocolate extract. For, with the bean extract the percentage of positive skin reaction is somewhat better. Regardless of the type of chocolate extract used there is no definite correlation between clinical sensitivity and skin tests. In some



of our cases where there was definite clinical sensitivity we obtained a negative or slight skin reaction. In other cases with negative sensitivity, slight or slight-plus reactions were elicited.

This work gives further evidence of the great pitfall in depending on skin tests for clinical sensitivity. What is true of chocolate is likewise true of many other foods. Great caution should therefore be exercised in evaluating skin tests, whether positive or negative, particularly when dealing with essential and basic foods. The unnecessary elimination of some of these foods often aggravates the condition of the patient, resulting in marked loss of weight. On the other hand a slight reaction may be of definite significance. Clinical trials of suspected foods and careful daily diaries will help establish true clinical sensitivity.

In our next experiment we will attempt to hydrolyze chocolate with pepsin, acid, and alkalis in an effort to note whether the split products of chocolate react differently on the skin of individuals who are clinically sensitive to chocolate.

## CONCLUSIONS

1. Chocolate extracts made from cocoa bean and cocoa shell gave more positive skin reactions than nibs, liquor or cocoa powder.

2. No definite correlation exists between skin reactions to chocolate and clinical symptoms.

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I am indebted to Dr. J. Kahn and Dr. A. Kantrowitz for their assistance.

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## STANDARDIZATION OF POLLEN EXTRACTS

(Continued from Page 296)

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# SENSITIVITY TO THIAMINE HYDROCHLORIDE

## Report of a Case

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VARIOUS types of reactions following the administration of thiamine hydrochloride have been reported during the past seven years. These reports attribute the reactions to the administration of thiamine hydrochloride to patients who had previously taken this substance with no ill effect. Skin tests have been recommended as a precautionary measure when the parenteral administration is contemplated.<sup>1,3</sup>

We have recently seen a case of sudden collapse following the intramuscular injection of 50 mg. of thiamine hydrochloride. This patient and seventy-three controls were tested with various dilutions of the vitamin.

### CASE REPORTS

In January, 1944, a previously healthy thirty-two-year-old seaman returned from a trip during which he had been engaged in repeated bombing attacks. He noticed nervousness, insomnia, loss of appetite, tremor of his hands and a startle reaction to sudden noises.

He received treatment in several cities for these symptoms and thiamine hydrochloride injections were given frequently. For three weeks following April 20, 1944, he was given 100 mg. intramuscularly every other day. During May and June of 1944 he received approximately ten injections of unknown dosage. From July 16, 1944 to August 4, 1944, he was given injections of 100 mg. every other day. On August 30, 1944, several minutes after an intramuscular injection of 50 mg. of thiamine hydrochloride, he developed severe itching and redness of his skin and eyes, dryness of the throat, severe shortness of breath with wheezing, respirations and collapsed. He recovered thirty minutes after administration of epinephrine. He was then sent to us for further study.

There was no history of allergy in the patient or his family. The physical findings were entirely normal. The blood smear showed 4 per cent eosinophiles.

### SKIN TESTS ON THE PATIENT

Skin tests were done on the patient and on seventy-three controls. All tests were read as follows:

- 4+ Pseudopods, wheal and flare
- 3+ Wheal and flare
- 2+ Flare 1 cm. or greater
- 1+ Flare less than 1 cm.
- 0 Same as saline control

Intradermal tests on the patient, with two brands of thiamine hydrochloride and with a solution of thiamine hydrochloride in physiological saline, were positive (4+) in dilutions of 50, 10, 5, 2.5, and 1 mg. per

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Permission for publication given by the Surgeon General, U. S. Public Health Service.

# THIAMINE HYDROCHLORIDE—SHAPERO AND GWINNER

c.c. Scratch tests with a solution of thiamine hydrochloride in physiological saline were positive in dilutions of 50, 10, 5 and 1 mg. per c.c. (4+, 4+, 3+, and 3+ respectively). Saline control tests were nega-

TABLE I.

Degree of Reaction	Concentration in mg. per c.c.				
	50	25	10	5	1
4+	2	2	0	0	0
3+	4	3	0	0	0
2+	10	11	14	5	0
1+	4	5	4	9	1
0	5	4	7	11	24

TABLE II.

Degree of Reaction	Concentration in mg. per c.c.				
	50	25	10	5	1
4+	1	0	0	0	0
3+	5	2	0	0	0
2+	12	12	7	1	0
1+	2	6	9	4	0
0	3	3	7	18	23

TABLE III.

Degree of Reaction	Concentration in mg. per c.c.				
	50	25	10	5	1
4+	0	0	0	0	0
3+	0	0	0	0	0
2+	0	0	0	0	0
1+	2	1	1	0	0
0	23	24	24	25	25

tive. Passive transfer tests gave a positive (4+) reaction in the 50 mg. per c.c. dilution but more dilute solutions were negative as compared to controls on the recipient.

Intradermal tests repeated after fifteen months during which the patient had no thiamine gave completely negative results in all dilutions.

## SKIN TESTS ON CONTROLS

Intradermal tests were done on twenty-five patients with thiamine hydrochloride solution in which chlorobutanol was used as a preservative. The number of cases showing the degree of reaction with each dilution are shown in Table I.

Intradermal tests were done on twenty-three cases with a solution of thiamine hydrochloride in physiological saline. The results are shown in Table II.

Scratch tests using a solution of thiamine hydrochloride in physiological saline were done on twenty-five additional cases. The results appear in Table III.

## INTERPRETATION OF SKIN TESTS

Comparison of the intradermal skin reactions in the case reported with those of the control groups (Tables I and II) indicates that dilutions of 50 mg. per c.c. and 25 mg. per c.c. are not reliable in testing for thiamine sensitivity. When dilutions of 10 mg. per c.c. and 5 mg. per c.c. are used, pseudopods and wheals are probably indicative of a sensitivity to the vitamin. In a dilution of 1 mg. per c.c. any reaction greater than the saline control should be considered significant, especially when a solution of thiamine hydrochloride without preservative is used.

Comparison of the scratch reactions in the case reported with those of the control group (Table III) indicates that pseudopods, wheals or flares greater than 1 cm. are indicative of thiamine sensitivity. This method of testing should be used in preference to the intradermal test when sensitivity to thiamine is suspected.

The value of a positive intradermal test with thiamine hydrochloride has been questioned. Kalz<sup>2</sup> found that all of thirty patients tested with a concentration of 10 mg. per c.c. developed an urticarial wheal. He concluded that skin tests with thiamine hydrochloride were not of diagnostic importance. Stiles<sup>11</sup> suggested that solutions of no greater concentration than 5 mg. per c.c. should be used for testing.

Previous reports describe two types of reactions to thiamine hydrochloride. The first is likened to the thyrotoxic state,<sup>4,5,12</sup> and is characterized by rapid pulse, irritability, insomnia, weakness, and trembling. The second appears to be allergic<sup>1,3,4,10</sup> and is characterized by itching of the skin and eyes, sneezing, urticaria, dyspnea, wheezing respirations, tinnitus, and vomiting. Two cases of severe sudden collapse with recovery after epinephrine<sup>8,9</sup> and two cases of sudden death<sup>6,7</sup> have been reported after the administration of thiamine.

Most serious reactions have occurred after the prolonged parenteral administration of the drug, suggesting that the sensitivity had been recently acquired. One death was reported after the fourth injection. Most of the patients observed mild reactions during the course of thiamine therapy, such as a wheal at the site of injection, itching of the skin, sneezing, wheezing, cough, dyspnea, perspiration, tinnitus, and vomiting, prior to subsequent severe reactions. The time interval elapsing between the onset of treatment and the appearance of these symptoms has varied considerably.

## SUMMARY

1. Sudden collapse followed an intramuscular injection of thiamine hydrochloride.
2. Positive intradermal and scratch tests were elicited on the patient and compared to seventy-three controls. Skin tests on the patient were completely negative fifteen months later.

3. Scratch tests are superior to intradermal tests in detecting thiamine sensitivity, for fewer false positive tests are obtained.

4. When an injection of thiamine is contemplated, the patient should be questioned concerning reactions from previous injections. In case of doubt, skin tests should be done.

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## INTRACTABLE BRONCHIAL ASTHMA

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## ATOPIC CATARACT

### Report of a Case with Tabulated Summary of Previously Reported Cases

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THE association of certain diseases of the skin and cataracts has been known for a long time. As far back as 1868 Rothmund<sup>38</sup> described four cases occurring in related families. The skin condition consisted of telangiectasia appearing during the early months of life over the face, gluteal region and the extremities; bilateral cataracts appeared in these children between the fourth and sixth years. Subsequently, ten or eleven similar cases were described, the skin manifestations being called poikiloderma atrophicans vasculare. In 1904 Werner<sup>49</sup> described another type of skin lesion, scleroderma, associated with the development of lenticular opacities. In Werner's syndrome the skin changes appear between the twentieth and thirtieth years and consist of thickening and hardening with atrophy of the subcutaneous tissue and glands; the feet are most severely affected, the legs, forearms, hands and face to a lesser degree. A total of thirty odd cases of scleroderma complicated by bilateral cataracts has been reported. In addition to the appearance of bilateral cataracts, other characteristics are noted in Werner's syndrome and reflect the part probably played by endocrine disturbances. In most of the cases reported there was early whitening of the hair; in many there were a juvenile build, alteration in the voice and eunuchoid features in the males.

#### NEURODERMATITIS AND CATARACT

The skin lesions of both Rothmund's and Werner's syndromes are very different from the lesions of the skin disease known as disseminated neurodermatitis. Not only are the papular, lichenified, disseminated or confluent lesions of neurodermatitis different from the lesions exhibited in the uncommon poikiloderma and scleroderma syndromes, but the entire background of the disease is different. However, an association of severe, long-standing neurodermatitis with the development of unilateral or bilateral cataracts has also been shown to occur. The first such cases were reported in the German literature by Andogsky<sup>2</sup> of Russia, in 1914. Since that time a total of twenty-seven cases has been reported in Europe, one in Australia and thirty-three in the United States. In view of the fact that neurodermatitis is a common skin disorder, the occurrence of cataracts in patients with neurodermatitis is obviously uncommon. For that reason the present case is being presented.

It is generally agreed today that disseminated neurodermatitis, in part, at least, belongs to that group of diseases placed under the heading of atopy, the most significant characteristic of which is the hereditary influence on the transmission of a state of hypersensitivity. Sulzberger<sup>42</sup>

# ATOPIC CATARACT—SACK

TABLE I. CASES PREVIOUSLY REPORTED IN THE AMERICAN LITERATURE

1 Author	2 Year Re- ported	3 Sex	4 Family History for Allergy	5 Age Der- matitis First Appeared	6 Age Cata- ract First Appeared	7 Interval Between 5 and 6	8 X-ray Ther- apy	9 Asso- ciated Allergies*	10 Per Cent Blood Eosin.	11 Skin Re- actions*	12 Cata- racts*
Davis <sup>15</sup>	1921	F		2	15	13		A.		D I	B
Daniel <sup>14</sup>	1935	F	+	1½	14½	13		Ur; R		—	B
		F	+	2 mos.	17	17	+	A.	15.5	+	B
		M	—	14	35	21	+	R, Ur	25	+	U
Sulzberger <sup>40</sup>	1936	M	+	Infancy	23	23	+	A, H.F.	16	+	B
Brunsting <sup>5</sup>	1936	F	+	6	16	10	+	H.F., R.	8-12	+	B
		M	—	Infancy	26	26	+	A, R.		+	U
		M	+	Infancy	21	21	+	H.F., Ur		+	B
		M	—	Infancy	21	21	+	R, H.F.	23	+	U
		F	?	12	23	11	None	Ur		+	U
		F	—	31	Rt. 24?			M?			U
		F	+	Infancy	Left 33	27	+	A, R		+	B
Mayo Clinic <sup>5</sup>		Rt. 38			Left 33	?	+	H.F.			B
		F									
		F									
		F									
		M									U
Cazort and Cook <sup>11</sup>	1938	F		7	15	8					B
Beetham <sup>8</sup>	1940	F	+	Infancy	27	27	+	H.F., A	4	+	B
		F	—	16	17	1		A	5	+	B
		F	+	Infancy	17	17		None	4-14	—	B
		F	+	2	17	15		None			B
		M	—	Infancy	17	17		None	10	—	B
		F	+	20	31	11		A		—	U
		F	+	15	29	14		A		+	U
		M	+	Infancy	Infancy	0		None			B
		M	+	6 mos.	14	13		H. F.		+	B
McDannald <sup>29</sup>	1943	M	—	Infancy	25	25		A		+	B
		M	?	5	18	13		A		+	B
		F	—	13	16-17	3	+	A		+	B
Cordes and Cordero- Moreno <sup>13</sup>	1946	M	+	6 mos.	15	14		A	11	+	B
		M	?	5	31	26					B
		M		47	49	2				+	B
		F		3	17	14		A, H.F.		+	B

\* A = Asthma  
H.F. = Hay Fever

R = Rhinitis  
M = Migraine

Ur = Urticaria  
D = Direct Testing

I = Indirect Testing  
B = Bilateral Cataracts  
U = Unilateral Cataracts

states that there is "strong presumptive evidence in favor of the important role of specific hypersensitivity in the production of all stages of atopic dermatitis." It should be pointed out that Sulzberger employs the term atopic dermatitis to include neurodermatitis. Sulzberger, Spain, Sammis and Shahon<sup>43</sup> state: "The above-mentioned results aid in establishing the picture of neurodermatitis disseminatus as an atopic disease of the most classical type, often with a surprisingly high degree of polyvalent hypersensitiveness." Many allergists<sup>16,44</sup> concur in this point of view.

In addition to vascular structures (which may represent the common anatomic denominator in most allergic reactions, including those of atopy), there are three tissues in which the disturbed physiology of allergy may take place. These are the skin, mucous membranes and, as some believe, smooth muscle. In the type of case being presented, another tissue is possibly the site of allergic reaction. This is the crystalline lens. The anlage of the human lens can be seen in embryos of 4 mm. as a thickening of ectodermal cells overlying the optic vesicle in the region of the forebrain. The lens, like the skin, therefore, is ectodermal in origin. It

# ATOPIC CATARACT—SACK

TABLE II. CASES PREVIOUSLY REPORTED IN THE EUROPEAN AND AUSTRALIAN LITERATURES

Author	Year Reported	Age	Sex	Skin Lesion	Age at Onset of Skin Lesion	Age at Onset of Cataract	Cataract*
Andogsky <sup>2</sup>	1914	27	M	Prurigo	3	25	B
		24	F	Eczema	10	22½	B
		25	M	Eczema			B
Vogt <sup>47</sup>	1922	28	M	Neurodermatitis	Early Youth	27	B
Kruz <sup>20</sup>	1924	22	F	Eczema			B
Lowenstein <sup>25, 27</sup>	1924	34	M	Neurodermatitis			B
		53	F	Neurodermatitis			B
		18	F	Eczema	8		B
Siegrist <sup>39</sup>	1928	18	F	Neurodermatitis	17	18	B
Ollendorf <sup>32</sup> and Levy	1932	23	M	Eczema	6	22	B
Oltmanns <sup>33</sup>	1932	23	M	Prurigo	8	23	B
		46	M	Prurigo	39	39	B
			M	Neurodermatitis	Early Youth		B
Metzger <sup>30</sup>	1932		M	Neurodermatitis	Early Youth		B
			M	Neurodermatitis	Early Youth		B
			F	Neurodermatitis	Early Youth		B
Laszlo <sup>22</sup>	1933	20	M	Prurigo	7	19½	B
Adler <sup>1</sup>	1933	26	M	Neurodermatitis	Childhood	25	B?
Gault <sup>18</sup>	1933	32	M	Neurodermatitis	20	22	B
Kugelberg <sup>21</sup>	1934	15	M	Ichthyosis and Neurodermatitis	6 months	15	B
		27	M	Eczema	5	25	B
		40	F	Neurodermatitis			B
Sannicandro <sup>39</sup>	1936	31	M	Neurodermatitis	22	29	B
Rollin <sup>27</sup>	1937	30	F	Eczema	Childhood	29	B
Tostevin <sup>45</sup>	1938	21	M	Neurodermatitis	Infancy	21	B
Milner <sup>51</sup>	1941	26	M	Eczema	Many years duration		B
Cibis <sup>12</sup>	1942	41	F	Eczema	4-5 weeks	36	B
		46	M	Eczema	10	39	B

\*B—Bilateral

would seem not far fetched to believe that where the skin has been the seat of prolonged, extensive and severe hypersensitivity, an organ allied to it embryologically might ultimately come to participate in the hypersensitive process. This is an idea which has been expressed repeatedly by those who have observed the association of neurodermatitis with cataract. This association constitutes the basis for describing this type of cataract as atopic, though there is additional, more concrete evidence to support that description.

## REVIEW OF FORMER CASES REPORTED

Table I lists all the cases of neurodermatitis associated with cataract that have been reported in the American literature to date. Table II lists the cases reported in the European and Australian literatures.

The cases are grouped separately because the data presented in the European literature are lacking in much of the detail, especially from the point of view of allergic interpretation, offered by the American reporters. Table I shows that the family history for allergy is positive in most instances, that many of the patients have allied allergies, that almost all the patients are in the adolescent or early post-adolescent stage when cataract develops, that in the few instances where blood eosinophile counts are mentioned, the count is 4 per cent more (in several cases being considerably higher than is found commonly in the allergic state), and that skin tests, where done, are usually positive. In the few cases where passive transfers were done, the presence of reagins in the blood of the



## ATOPIC CATARACT—SACK

patient is demonstrated by positive reactions in the sensitized sites of the substitute.

The two most striking features in the development of atopic cataracts are (1) the long interval that intervenes between the first appearance of the skin lesion and the appearance of the opacity and (2) the speed with which the cataract matures once it comes on. Once the cataract begins to develop, it may mature completely in a few weeks. The changes occurring in the lens are irreversible.

There are several arguments which may be offered to refute the possible allergic nature of the cataract complicating neurodermatitis. Most of them can be adequately met. It may be asked, for example, why the associated cataract appears so infrequently if neurodermatitis as a manifestation of allergy occurs so commonly. It will be noted from column 7 of Table I that the interval between the first appearance of the skin lesion and the development of the cataract is a long one, being on the average, fifteen years. This means that the dermatitis must be of approximately fifteen years' duration, continuously or intermittently, before the lens is sufficiently traumatized allergically (i.e., sensitized) for the cataract to develop. In the majority of cases, atopic dermatitis does not last that long; the lesion clears up spontaneously or its disappearance is hastened by medical management long before fifteen years elapse. Again, it may be asked why the cataract is not invariably bilateral. Actually it is not the invariable finding in allergy to have the disturbance universal in its distribution. Thus, in chronic recurrent urticaria, though the lesions may be spread diffusely over the body, there may still be large areas of skin uninvolved. In perennial vasomotor rhinitis one occasionally sees only one side of the nose affected. Most classically, in migraine only one side of the head is often involved in an attack, and that, commonly, the same side in each attack. It is quite possible, too, that if the cases with unilateral involvement were followed a little longer, the other eye might have been found to have become involved. The objection that has been most often raised against the belief that this type of cataract in young people is atopic, is the fact that many of the patients concerned have received x-ray therapy for their chronically inflamed skin. It is known that x-rays can produce degenerative changes in many tissues, including the crystalline lens. That x-ray therapy in the cases with which we are dealing is not the cause of the cataract is supported by two considerations: (1) there are cases in which x-rays had never been used; (2) in *acne vulgaris*, a skin disease much more common than neurodermatitis and for which x-ray is frequently employed, cataract is not seen. This fact has been pointed out by others.

Among the factors which have at times been implicated in the causation of this type of cataract, one may mention dietary deficiencies, endocrine dysfunction and disturbances in the nervous system. Beetham<sup>3</sup> found his patients undernourished and underweight; eight of his ten

cases averaged 20 per cent underweight. Goeckerman in discussing Brunsting's<sup>5</sup> paper also emphasizes the inadequate nutrition of patients with atopic dermatitis. Other writers who have reported cases of cataract associated with neurodermatitis have not stressed this point. Beetham<sup>8</sup> himself states that although cataracts and dermatitis can be produced experimentally in animals by vitamin deficient diets, such causal relation has not been proved for humans. The part played by endocrines is uncertain. In Werner's syndrome the abnormality in build, the change in voice, the early whitening of the hair and the eunuchoid features in males point to dysfunction of the endocrine system. In cataract with neurodermatitis the evidence is much less suggestive. Bellows<sup>4</sup> points to the histologic similarity to cataracts of known endocrine origin, the youth of the patients, the rapid maturation and the commonly bilateral involvement as indicating a possible endocrine causation. However, several of these factors are also common in allergy. Investigations from the chemical and clinical points of view do not support the endocrine explanation. The German literature, particularly, emphasizes the probability that malfunction of the endocrines is responsible for the formation of the cataract. Very little evidence is offered to justify that contention. Least of all can the autonomic nervous system be directly implicated, notwithstanding the well-recognized irritability of many patients with long-standing pruritic lesions.

Of the total of sixty-one cases reported to date, thirty-five were males and twenty-six were females; fifty had bilateral cataracts, seven had unilateral cataracts, and in four the distribution is not mentioned. All the European cases had bilateral cataracts; the average age at which cataract developed among them, where the age is given, was twenty-five years. The data are too meager for calculating the interval between the first appearance of the skin lesion and the appearance of the cataracts in the European cases. The average age at which the cataract appeared among the American cases was twenty-two years, and the average interval between the very first onset of the skin lesion and the appearance of cataract was fifteen years.

#### THEORIES OF THE MECHANISM OF ATOPIC CATARACT FORMATION

In seeking an explanation for the mechanism whereby the atopic cataract is formed, Daniel<sup>14</sup> in 1935 stated: "A fine change in function of these epithelial cells of the ciliary body, in the content of the aqueous fluid or in the level of permeability and selectivity of the capsule of the lens can readily be reasoned to interfere with the efficient metabolism of the lens and its transparency, thereby producing a cataract in an otherwise normal eye." Woods,<sup>14</sup> in discussing this suggestion, criticized the assumption that the cells of the ciliary body might be involved and that there was a change in the contents of the aqueous. Nor was Woods,<sup>14</sup> a pioneer in the work on the chemistry and immunology of lens proteins,

too ready to accept the hypothesis that a change in the permeability of the lens capsule, resulting from the participation of the lens in the allergic process, allowed passage of elements from the normal aqueous through the altered capsule, causing precipitation of lens protein. Beetham<sup>3</sup> removed aqueous from the eyes of two of his reported patients and did intradermal tests with this material on the same patients. The reactions were negative. Since anything reaching the lens would have to be present in the aqueous the assumption that there was an exciting antigen in the aqueous might make one expect a positive skin reaction with aqueous. If a nonantigenic yet traumatizing constituent of the aqueous passed through the capsule, a positive skin reaction would not take place, but as will be pointed out later, the evidence does not indicate that the permeability of a cataractous lens differs from that of a normal lens. Nor has it been demonstrated conclusively in other manifestations of allergy, in spite of occasional, uncritical reports to the contrary, that the human can be sensitized to the *normal* products of his own secretion. Brunsting did a skin test on one of his affected patients, using this patient's own lens material as the test substance. The reaction was negative.

#### IMMUNOLOGY OF LENS PROTEIN

The current status of the immunology of lens protein is presented in excellent summary by Bellows.<sup>4</sup> The literature on the immunology of lens protein was conflicting, some investigators reporting sensitization of animals to their own lens substance and others stating their failure to effect this, until the work of Woods and Burky<sup>51,52</sup> was reported, beginning in 1927. The experimental results of these men supported Uhlenhuth's<sup>46</sup> original observation that lens protein is organ specific and not species specific. They were also able to corroborate and extend the findings of Mörner<sup>32</sup> who had identified alpha and beta crystallins in whole lens. Burky and Woods<sup>8</sup> have shown that lens protein is complex and consists of at least three different proteins excluding the capsule. These proteins—alpha, beta, and gamma crystallins—are chemically and immunologically distinct. The alpha fraction is the most active antigenically and is regarded by Woods, Burky and Woodhall<sup>53</sup> as the true organ specific substance of whole lens, for only that fraction can act as an antigen in the homologous animal. When the alpha fraction is combined with the other fractions, as in the whole lens, it is not antigenic in the homologous animal because the inert beta and gamma crystallins inhibit the action of the alpha fraction. Beta and gamma crystallins are inert in homologous species. Woods and Burky<sup>52</sup> state that there is little evidence that lens protein from an unruptured capsule exerts any antigenic activity. After rupture of the capsule some individuals develop cutaneous sensitivity to lens protein, their own lens serving as the sensitizing antigen. This may help to explain what occurs in phacoanaphylactic endophthalmitis following surgery for cataract in some instances.

In 1922 Verhoeff and Lemoine<sup>47</sup> ascribed to allergy the ocular inflammatory reaction occasionally set up postoperatively following cataract extraction, stating that the residual injured lens protein served as the exciting antigen. On the basis of the experimental facts supplied by Woods and Burky,<sup>51,52</sup> it has been reasoned that a loss or disappearance of beta gamma crystallins as the result of incision into the capsule releases the antigenic alpha fraction from its inhibition so that it becomes active. Burky<sup>6</sup> has also demonstrated that antigenicity of lens substance can be enhanced by staphylococcus toxin for he was able to produce cutaneous sensitivity to lens substance in rabbits by repeated and coincident injections of staphylococcus toxin and lens substance and, subsequently, by needling the eyes of such sensitive rabbits, produce the clinical and histologic picture of phacoanaphylactic endophthalmitis as seen in man.

Normally, and usually even after injury to the lens capsule, a positive skin reaction with lens substance is not obtained because active alpha crystallin within the subject's lens, being inhibited by the beta-gamma fractions, has been unable to sensitize the subject. If the inhibiting elements are lost or are present only in small amounts as the result of surgical intervention or otherwise, the antigenicity of the alpha fraction may become operative and thus sensitize the individual. If the individual is sensitive to lens protein because of such imbalance of fractions, he may give a positive skin test, and ocular reactions may follow capsulotomy. If the individual is not sensitive to start with, he may be rendered sensitive after capsulotomy so that an allergic inflammatory change may ensue after injury to the second lens. Burky and Woods<sup>9</sup> found eleven out of sixty-four patients with cataract gave a positive skin reaction to lens substance and found no positives among seventy-five normals. It is not difficult to understand the negative skin reaction obtained by Brunsting<sup>5</sup> on the one cataractous patient on whom the test was done.

#### LENTICULAR CAPSULE

The lenticular capsule is a semi-permeable membrane which allows the passage of all electrolytes—water, salts, and other crystalloids—and also small and medium-sized colloidal particles. It is through the capsule that substances reaching or leaving the lens must pass. Nutrition and elimination are effected through the aqueous which is formed by the ciliary body. The lens has no circulation of its own. Physiologically, transparency of the lens is dependent upon the maintenance of capsular permeability. The capsule may exhibit considerable fluctuation in permeability depending upon changes in its environment. However, it has not been established definitely that the permeability of a cataractous lens differs from that of a normal lens. Thus Gifford, Lebensohn and Puntenny<sup>19</sup> found the permeability of the capsule in five cataractuous lenses from human beings was approximately the same as that of normal rabbit lenses. The original theory of Löwenstein,<sup>26</sup> that capsular permeability

increases with age so that senile cataract might be regarded as a product of the more ready passage of toxic substances into the lens or the loss of nutritive elements from the lens, is not substantiated by the later experimental findings of Friedenwald<sup>17</sup> and others. Friedenwald has shown that the permeability of lens capsules from young animals is greater than that of the lens capsules from adult animals. Variations in osmotic pressure and hydrogen ion concentration have been ineffective in producing cataract *in vitro*. In mature naphthalene cataract, Gifford, Lebensohn and Puntenny<sup>19</sup> were able to find no increase in the permeability of the capsule. Furthermore, Woods and Burky<sup>52</sup> have pointed out that the available evidence indicates that the fully developed lens capsule is impermeable to antibodies.

Bearing all these fundamental facts in mind, one cannot at this time postulate a change in capsular permeability to the contents of the aqueous as the immediate physical cause for the cataract formation in the entity under discussion.

#### CASE REPORT

The case herein reported is that of a girl, seventeen years old, who was seen for the first time on May 13, 1946. She was referred by her family physician because of an extensive rash over her face, neck, elbows and behind her knees. The patient's paternal grandmother had asthma and a paternal aunt had hay fever. At the age of two, a rash had appeared over the face, elbows and popliteal spaces of the patient. The rash over the elbows and knees would come and go and thus been intermittently present for the last fifteen years, being worse during the winter. The rash over the face initially lasted a few weeks or months, disappeared, appeared again when the patient was three years old, again lasting a few months, and then did not recur until the patient began to menstruate at about thirteen years of age. The rash at this time involved the neck and chin and only slowly came to cover the face, so that it was not until she was fifteen that the whole face became involved.

The rash had always been itchy and had been responsible for much scratching. During the past four years the rash had been worse just before the menses. From February, 1944, to May, 1944, when the patient was fifteen, she was given x-ray therapy on three occasions to the face, neck and cubitals for a total of 60 roentgens. In February, 1945, as the result of a routine school examination, the patient consulted an optometrist who found that her visual acuity for distant vision was 20/30 in the right eye and 20/20 in the left eye. In September, 1945, her vision was again tested and was again found to be 20/30 in the right eye and 20/20 in the left.

At the age of six the patient had had pneumonia, and at the age of eight a tonsillectomy and adenoidectomy had been done. There was no other significant past medical history.

On April 11, 1946, the patient noted that the glands of the neck and those behind the ears were swelling. The following day her temperature rose to 103° and small blisters appeared on the chin and around the mouth. These blisters ruptured and became crusted. About one week after the glands in the neck were observed, the scalp became extensively covered with large pustules which attained the size of marbles, ruptured, oozed and crusted. Numerous such lesions appeared throughout the scalp. From April 12, 1946, to May 5, 1946, the temperature fluctuated between 100° and 103°, but the patient did not feel very ill. The tempera-

ture returned to normal on May 5 and remained so. During this period of three weeks she was seen several times by her family physician. The only medication taken by the patient was calcium salts.

When the patient was seen on May 13 she did not appear acutely ill. The temperature was 98°, pulse 80, blood pressure 96/60, weight 112 pounds. The scalp was diffusely covered with large numbers of heavy crusts up to 1 centimeter in diameter; many of them were elevated several millimeters. No fresh pustules were seen. Many crusted scales were trapped in strands of hair. About half way down along the anterior margin of the left sternocleidomastoid muscle there was a mass of matted glands. Individual nontender glands were easily palpable on the right side of the neck, over the posterior surface of the neck and behind both ears. The face was covered with small excoriated papules; the skin of the neck was thick, rough and deep brown in color. The skin over the flexures of the elbows and knees presented the characteristic lichenified appearance of longstanding neurodermatitis. A silvery white opacity was noted in the left eye. This was a mature cataract. The right lens showed linear striae composed of punctate opacities in the anterior cortex producing the effect of wheel spokes. This was an incipient cataract. Visual acuity in the right eye was 20/30. With the left eye the patient could not recognize moving fingers at a distance of a few inches; she did, however, have perception of light. The fundus of the right eye was normal. Tension in both eyes was normal. Until the time of the examination the patient was not aware that she was blind in the left eye. The hairs of the eyebrows were broken and stubby due to the constant rubbing to overcome the itching. The rest of the examination was not significant.

The Wassermann test and urinalysis were negative, as was an x-ray of the chest taken the end of May, 1946. The white blood count on May 16 was 10,500 with 4 per cent eosinophiles; the remainder of the differential was normal. On May 20 a second blood smear showed an eosinophilia of 5 per cent. Direct intradermal skin testing on what appeared to be relatively normal skin of the arms gave slight to moderate reactions to practically all seventy food and inhalant extracts employed. Indirect testing (passive transfer) was therefore done. Indirect testing confirmed many of the direct tests. Reactions to the following substances were passively transferred: cottonseed, cow epithelium, dust, feathers, horse epithelium, horse serum, kapok, orris root, rabbit epithelium, silk, wool, timothy pollen (0.1 mg. N per c.c.), plantain pollen (0.1 mg. N per c.c.), tree pollens (0.1 mg. N per c.c.), cherry, grapefruit, orange, peach, strawberry, cinnamon, ginger, mustard, gum chicle, corn, rye, egg white, lamb, herring, oyster, salmon, chocolate, milk, almond, asparagus, celery, green peas, lima beans, sweet potato, and tomato.

The patient was operated upon on August 3, 1946. A combined extracapsular extraction of the left lens was done. The patient made an uneventful recovery. On September 3, 1946, vision in the right eye was 20/30 and in the left eye the patient had light perception correctible to 20/70 by means of a plus 11 sphere combined with a .50 cylinder, axis 40°. Both fundi were normal and the tension in both eyes was normal.

One of the striking results of skin testing in the former reports where skin testing was done is that though there were positive reactions to many foods and inhalants, silk among the inhalants and egg among the foods occurred most commonly. Reactions to these two substances were positive in the above case, both on direct and indirect testing.

During the three weeks that the patient was under observation, the lesions in the scalp continued to diminish, so that by June 3 the scalp was almost clear. The glands in the neck also had entirely disappeared during this time. The most im-

pressive feature of the patient's course, however, was the improvement that took place in her old skin lesions. The skin of the face, neck, elbows and knees became much smoother, softer and more pliable, a change that may be attributed in part most likely to the elevated temperature experienced by the patient over a period of about three weeks. In smaller part the improvement may have fitted in with the history that the lesions were always better with the onset of warm weather. One must, of course, remember that marked fluctuation in the severity of neurodermatitis is a very common occurrence. The nature of the pyoderma of the scalp is not known. None of the drugs known to cause cataract was used by the patient before her acute illness or during it. The general constitutional diseases such as diabetes and nephritis occasionally causing cataract were excluded as possible causes.

The prognosis in cataract associated with neurodermatitis is good if surgery is skillfully effected. Postoperatively vision in the affected eye or eyes is usually restored by means of correcting lenses.

## SUMMARY

A case of neurodermatitis of fifteen years' duration in a girl of seventeen in whom bilateral cataracts developed, one reaching maturity in a period probably not exceeding seven months at most, is presented. The case fits into an entity previously described by a number of observers in both the European and American literatures. There is evidence to believe that the cause fundamentally responsible for the long-standing neurodermatitis is also responsible for the formation of the cataract and that atopy is probably involved in both. The mechanism whereby the cataract is produced is not known. The available experimental evidence does not at this time support the contention that altered permeability of the lenticular capsule is the immediate mechanism by which the opacity is formed.

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# THE SIGNIFICANCE OF CHRONIC BRONCHITIS IN INFECTIOUS BRONCHIAL ASTHMA

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THE capacity of sulfonamides and antibiotics to eradicate acute pulmonary infections of various types has given new hope for a causal therapy of chronic bronchitis. Encouraging results from prolonged administration of penicillin as aerosol<sup>3,17,47</sup> indicate that the transition from certain acute to chronic bronchopulmonary infections may be avoided. Thus, the incessant pleas for prevention of chronic bronchitis and bronchiectasis by early elimination of pulmonary infections, may find, at least, their realization.

The recognition of developing nontuberculous infections in the lower respiratory system is still a challenge to the medical profession. The frequent failure of early diagnosis is due mainly to misleading symptoms and associated conditions. Upper respiratory infection is frequently present in patients with chronic bronchitis, and is usually held to be the primary cause. Most confusing are asthmatic manifestations which are commonly interpreted as true bronchial asthma, the existing pulmonary infection being considered as secondary to an allergic condition.

In the course of treating respiratory infections with penicillin aerosol, the author has been impressed by the improvement or disappearance of asthmatic symptoms in many cases which had been considered as bronchial asthma.<sup>17</sup> As a rule, these patients were children or young adults; although in some of them the condition had existed for several years, none of those who recovered had evidence of gross pathological changes such as bronchiectasis. In all of these asthmatic patients the disease had been initiated by an acute, severe respiratory infection.

Observations of this kind emphasize the importance of proper and early evaluation of etiological factors in infectious asthma. Most publications on this subject do not consider adequately the significance of acute respiratory episodes in the beginning of this type of asthma, and do not seem to realize the implications for a rational therapy of this serious disease. In view of this, the following study attempts to establish the actual role of bronchopulmonary infection in the picture of infectious asthma from the onset to its end.

In recent years, it has been realized that asthma is not always due to allergy but that it may be also a symptom in other conditions without allergic background. The postulate of ten years ago that "who wheezes has asthma" as a manifestation of allergy,<sup>51</sup> has been replaced by the warning "all is not allergy that wheezes." It is now generally acknowl-

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edged that cardiac conditions can produce asthmatoïd respiration, and that asthma occurring in silicosis, tuberculosis and pulmonary malignancy should be considered apart from true bronchial asthma.<sup>49</sup> The same stand has not been taken, so far, in nonspecific pulmonary infections with asthmatic symptoms. Although chronic bronchitis and bronchiectasis are known to produce asthma without the presence of allergy,<sup>2,9,37,55,60</sup> this type of asthma is usually not differentiated sufficiently from bronchial asthma.

Occasional publications, older as well as recent ones, did stress the close relationship between pulmonary infection and asthma. Ever since clinicians of the nineteenth century had observed that certain acute respiratory episodes could be held responsible for the "humid asthma of practitioners with chronic mucous catarrh" (Laennec)<sup>4,19,31,44</sup>, numerous studies have confirmed pertussis, measles, pneumonia and influenza as likely causes in many cases of asthma.<sup>6,7,22,26,38,43,46</sup> The significance of unresolved pulmonary infiltrations in the history of some of these patients has been repeatedly emphasized.<sup>22,38</sup> Moreover, the dominant feature in a high percentage of cases diagnosed as bronchial asthma appeared to be chronic bronchitis.<sup>21,28,32</sup>

Although these factors point toward infection as the primary etiology of infectious asthma, the tendency to interpret this condition as an allergic manifestation still prevails, and seems even to gain ground.<sup>15,57</sup> A history of eczema or pollinosis in a patient with the infectious type of asthma is regarded, *a priori*, as evidence of its allergic etiology. In absence of the usual type of allergy, the presence of eosinophilia in the patient's blood and of allergy in his family suffice for the assumption that hypersensitivity has been responsible for the asthmatic condition.<sup>11</sup> Respiratory infections, *per se*, are not believed to cause asthma in any individual. It is assumed that these infections sensitize an allergic or potentially allergic individual to bacterial and other proteins, thereby producing asthma by virtue of an immunological mechanism. Pneumonia and other respiratory episodes are considered to be forerunners of true bronchial asthma in patients with allergic background only,<sup>57</sup> and irreversible lesions in chronic asthma are attributed to longstanding allergy of some kind.<sup>10,56</sup> Thus, bronchitis, bronchopneumonia and bronchiectasis, if associated with asthmatic manifestations and one or another of the findings allegedly indicative of allergy, are thought to be initiated by allergic reactions.<sup>35,54,61,62</sup> Consequently, early desensitization has been advocated in allergic and possible allergic children after their being affected by respiratory infections in order to protect them from developing bronchial asthma.<sup>38,57</sup>

This conception of allergy in infectious asthma is not satisfactory from a clinical point of view; it does not illuminate certain features of this condition, and it tends to obscure the distinction of chronic bronchitis from bronchial asthma. The existing confusion in this respect is best reflected

in the various classifications of bronchial asthma in which intrinsic asthma, chronic asthma, asthmatic bronchitis, and infectious or bacterial asthma are terms applied to conditions which are, rather arbitrarily, assigned to allergy, to infection and to both.

It was believed that an investigation of cases grouped as infectious asthma might answer the question whether this disease should be considered as mainly due to infection or to allergy. As mentioned before, this problem appears of major importance with regard to proper management of infectious asthma in its early stage.

The basic material for this study was a series of 235 records of patients who had been hospitalized at the Genesee Hospital between 1935 and 1945 with the diagnosis of bronchial asthma. From these cases, in which no patient with heart disease, silicosis, tuberculosis, and the like was included, 100 with infectious asthma were selected for further investigation. The selection was made in accordance with a recent classification of asthma<sup>16</sup> in which essential characteristics of infectious asthma are: an acute respiratory infection which initiates the condition, and respiratory infection dominating the picture through its course. Using the same classification, patients with infectious asthma and coexisting allergic manifestations are designated as mixed atopic and infectious asthma. They are also included in this series.

In all 100 of these asthma cases, a severe respiratory infection was assigned by the patient or by relatives as its cause. Moreover, the course of events, traced meticulously, proved that this infection had initiated a respiratory disease, with asthmatic manifestations following sooner or later.

In forty-four of the 100 patients, the onset could be directly related to a specific illness; namely, pertussis in thirteen, pneumonia in seventeen, and influenza in fourteen cases. In the remaining fifty-six, less specifically diagnosed infections, such as bronchitis, bad chest cold, grippe, et cetera, were found to have initiated the asthmatic condition. It was inferred from the records of many patients that infections diagnosed as pneumonia and chest colds had in reality been pneumonitis of the non-pneumococcal type. Frequent occurrence of pneumonia in early childhood, occasional designation as unresolved pneumonia, and recurrence of a severe "grippe," spoke definitely for that type of subacute pulmonary lesions which may follow measles, influenza and the like. Of fourteen patients where influenza could be held responsible for the infectious asthma, eleven were sufferers from the epidemic type occurring during the first World War.

The age groups, in which the patients with infectious asthma had been hospitalized during the past ten years, can be noted in Table I. The age groups in which these patients had contracted one or the other of the initiating infections can be seen in Table II.

It becomes obvious from Tables I and II that a little more than half of all cases with infectious asthma had been hospitalized at an average age

# CHRONIC BRONCHITIS—FINKE

TABLE I. AGE AT TIME OF  
HOSPITALIZATION

<i>Age Group</i>	<i>Number of Cases</i>
Under 10 years .....	16
10-20 .....	3
20-40 .....	28
Over 40 .....	53

TABLE II. AGE AT ONSET OF INITI-  
ATING INFECTION

<i>Age Group</i>	<i>Number of Cases</i>
Under 10 years .....	31
10-20 .....	6
20-40 .....	33
Over 40 .....	30

of over forty, but that in 70 per cent of the whole group the actual onset of the disease occurred before the age of forty. The average age of onset of infectious asthma in this series was 22.3 years.

In ten of the thirty-one patients in whom infectious asthma had its onset in the first decade of life, pertussis was the assigned cause, and in six more, pneumonia. Among the thirty-three patients in whom asthma originated at the age of twenty to forty years, there were ten who developed this condition following influenza.

Of eight patients who died in the hospital during the past ten years from infectious asthma, four were under the age of forty years and four beyond that age at the time of death. However, in five of the eight deaths, the onset of infectious asthma occurred before the age of ten, and in only one after forty.

Allergy in some form had existed or was suspected in twenty-two patients. In sixteen, clinical allergy had been present. In eight of these sixteen patients, the allergic manifestations were of the usual type, such as pollinosis and eczema. In seven others, hypersensitivity to aspirin alone existed, and in one patient both pollinosis and aspirin hypersensitivity could be found. In thirty-eight patients skin tests were done; nine showed definitely positive skin reactions. In five more patients, the result was considered as questionable.

In twenty-eight patients the family history revealed the presence of atopy or of possible atopy in one or more relatives. The eosinophil count was normal in most cases with coexisting allergic manifestations, as it was in the great majority of this group. In some patients without any evidence of hypersensitivity, excessive eosinophilia was present.

The relationship between previous or present allergy and the asthmatic condition was held to be of great significance in this series. The asthma of the eight aspirin-sensitive patients was of an especially severe character. However, it was different from the infectious asthma, taken as a whole, only inasmuch as salicylates, frequently also codeine and morphine, aggravated the existing asthmatic condition. Two of the eight aspirin-sensitive patients died in the hospital. Among the eight patients, who at some time had presented common allergic manifestations, were three who developed pollinosis several years after a chronic bronchopulmonary infection had become evident. Two had been diagnosed as bronchial asthma only after hay fever had appeared. In the remaining five patients, allergic conditions preceded infectious asthma; in two cases, intervals of six years and eighteen years, without respiratory symptoms, had elapsed

before infectious asthma developed. Three patients had suffered from seasonal allergic rhinitis and asthma shortly before, or at the time of, infectious asthma. In all five with preceding or present allergy, a respiratory infection of severe character occurred before the appearance of infectious asthma.

The most striking feature in all patients with infectious asthma was the clinical evidence of a gradually progressing infection of the bronchopulmonary system. The sequence of events is best demonstrated in the records of patients who had been observed over many years. Tonsillectomies had been performed in children with periodic respiratory episodes following pertussis or bronchopneumonia. Not infrequently, patients had been under observation for tuberculosis in clinics and sanatoriums. Months or even years after the acute respiratory infection, the progressing condition had been diagnosed as bronchial asthma, asthmatic bronchitis, or intrinsic asthma. Asthmatic paroxysms with free intervals, although present, did not dominate the picture. Persistent cough with purulent, at times malodorous or bloody sputum, indicative of suppurative and destructive changes, was the most troublesome symptom. Variations in the picture were, as a rule, due to the extent of the underlying pulmonary changes. The majority of patients were admitted during one or more acute exacerbations. Consolidations in the lungs were frequently present during these acute febrile episodes, usually diagnosed as pneumonia. In recent years, atypical pneumonia was noted as the diagnosis in a number of patients. Staphylococci and streptococci were usually predominant in the sputum of these patients. Unlike lobar pneumonia, the onset and termination of the pulmonary lesion was gradual. Frequently, there was evidence of previous damage of the respiratory system, and the new exacerbation left its marks in the affected lung.

Thirty-nine among forty-six patients, of whom roentgenograms had been taken, showed definite, and often extensive, pathologic lesions such as marked basal fibrosis with pleural involvement and atelectasis. Emphysema, chiefly of the patchy, compensatory type, was the rule. In two cases, one case a pneumothorax, and the other massive collapse of a lung, large emphysematous blebs were found.

Lipiodol studies were done on eight patients. Five presented bronchographic evidence of bronchiectasis, although many more patients had symptoms usually held characteristic of this condition.

The severity of the existing pulmonary lesions was not necessarily related to the duration of the disease. In twenty patients, who dated the onset of the asthma at least ten years earlier, a relatively mild course and the absence of marked gross lesions could be observed. On the other hand, eight patients with duration of their illness from two to five years presented extensive pulmonary changes. It seemed that the seriousness of the preceding acute illness had a major bearing on the course and the

clinical picture. Among eight roentgenograms taken of patients whose asthma began following influenza, seven showed extensive damage of the lungs. In nine others taken of those who developed asthma after pertussis, six revealed the same type of changes, indicating a severe, chronic, nonspecific bronchopulmonary infection.

Purulent lesions of the nose and sinuses were present in thirty-four patients. In at least half of these, the upper respiratory infection had occurred simultaneously with, or following, the appearance of lower tract respiratory infection.

The response to therapeutic measures of any kind, in all cases which could be followed, was, at best, temporary. This is also demonstrated by the periodic admissions of a great number of patients. Their conditions could generally be found to have become worse with every new acute exacerbation. Neither surgical measures on nose and throat, nor routine allergic and other treatments, although applied initially, prevented to an appreciable extent the progress of the disease.

Eight of the patients with infectious asthma died in the hospital during the ten-year period. The dominant feature at the time of their death was a chronic bronchopulmonary infection, as it had been during life. They died, as a rule, with clinical manifestations of asphyxia, and, not infrequently, with toxic symptoms. In three cases which came to autopsy, the anatomic findings in the lungs were essentially fibrotic-bronchiectatic lesions with suppuration in bronchi and fibrinous pleurisy. Two among the eight cases had evidence of possible allergy in the past, but in none was this present at the time of death.

In five of those eight patients who died, morphine was given before death. In at least three of them, the course of events was very suggestive of a close relationship between the administration of morphine and the death of the patients.

In one of the aspirin-sensitive patients, death was attributed directly to a dose of aspirin. Forty-five minutes after taking the drug he collapsed, and on the following day died, supposedly from anaphylactic shock. However, the life story, the clinical picture, and the anatomic findings of this patient were also characteristic of infectious asthma, without evidence of the usual type of allergy. His disease apparently began after an attack of influenza in 1918, and developed gradually to chronic bronchopulmonary infection with bronchiectatic-fibrotic lesions.

#### DISCUSSION

The study of one hundred cases of infectious asthma, in which a correlation of the characteristic features was attempted, indicates that the condition is fundamentally chronic bronchitis, with asthma as one of the many symptoms present. The etiological background of infectious asthma is a nonspecific chronic bronchopulmonary infection originating from

certain acute respiratory diseases. The same factors are involved in a great number of cases which are commonly labeled chronic bronchitis, with or without marked asthmatic symptoms.

Naturally, respiratory infection may have a different significance in certain patients with extrinsic and intrinsic asthma. However, in many, regardless of their being designated as asthmatic bronchitis, bronchial asthma, intrinsic or bacterial asthma, bacterial infection of the lower respiratory organs is undoubtedly the direct cause. They usually present all or most characteristics of infectious asthma if the necessary details have been investigated. Respiratory infection was the most conspicuous feature in the majority of Rackemann's cases with intrinsic asthma.<sup>39,40</sup>

The general belief that infection with bacterial allergy tends to take the place of the usual type of allergy with advancing age is not substantiated by actual figures from this study and from other investigations. In Rackemann's group of intrinsic asthma,<sup>39</sup> as well as in Unger's of chronic asthma,<sup>57</sup> the onset of the disease occurred in the majority under the age of forty, and in a rather high percentage in childhood. Observations, like Bivings'<sup>55</sup> and Taylor's,<sup>52</sup> on the frequent occurrence of a definitely infectious type of asthma in children, are confirmed by general experience. The surprisingly high incidence of chronic bronchopulmonary infection in young asthmatic soldiers, as found by Zoss,<sup>63</sup> speaks also against the assumption that chronic bronchitis is present chiefly as a complication in elderly patients with longstanding asthma.

The misconception that intrinsic asthma, apparently due to infection, is prevalent after the age of forty can be attributed to the fact that frequently there is a latency of several years between the onset of infection and the appearance of asthmatic symptoms. It is not unusual that a patient, whose asthma started in the later part of life, will admit after repeated questioning that he had been affected by "cigarette cough" for many years, or that he suffered since childhood from frequent colds which he "had a hard time to throw off." Usually, it can be elicited that an acute respiratory infection had initiated the respiratory symptoms.

Pertussis and bronchopneumonia, complicating measles and other infectious diseases, are known to be frequent, although not always appreciated, causes of chronic bronchitis and of bronchiectasis.<sup>18,25,29,34,48</sup> This explains why early childhood is a danger period also of infectious asthma. Later in life, influenza and severe pulmonary infections of similar character, not bound to a particular age, are important factors in the onset of this condition,<sup>22,36</sup> the nature of which in children is essentially the same as in adults.

The sequence of events usually begins with subacute pulmonary infiltrations following the acute respiratory infections, and leads frequently to that disease which has been studied for many years under various terms such as fibroid disease of the lung, chronic pulmonary catarrh, chronic pneumonia, chronic interstitial fibrosis, and the like.<sup>33</sup> Bronchi-

ectasis may or may not accompany the pyogenic process; if it occurs, it may develop early or may be found as an end stage after many years. It was in a child who had been affected by whooping cough, and in an old woman who had suffered most of her life from a chest ailment that Laennec demonstrated for the first time dilatation of the bronchi.

The causal relationship between acute initiating infection and the clinical picture of the asthmatic condition is more impressive in this series of selected patients with infectious asthma than in currently published groups comprising asthma of all types. It ought to be mentioned here that Peshkin<sup>38</sup> found all of the nonsensitive asthmatic children, in whom respiratory infection was the assigned cause, suffering from chronic bronchitis. Among patients diagnosed by Thomas and Taylor<sup>54</sup> as allergic bronchitis, almost half of the cases related their condition to pertussis, pneumonia and influenza, and in 14 per cent bronchiectasis was evident or suspected. Harkavy's<sup>22</sup> patients, whose asthma developed following unresolved pneumonia, belonged to the nonsensitive type.

It is justifiable to state that asthma, which develops after certain acute infections of the lower respiratory system, is entirely different from bronchial asthma due to allergy. The bronchopulmonary lesions in infectious asthma may and do cause asthmatic paroxysms which however are not related clinically to known allergens. Epinephrine does not act in infectious asthma as promptly as it does in an attack of allergic asthma. The pathologic changes in the former are mainly irreversible, whereas allergic reactions are, as a rule, transient in character. However, the favorable response to epinephrine of an asthmatic patient should not be evaluated as proof of an atopic background. Many cases with bronchitis and even with bronchiectasis, without evidence of allergy, may also experience great relief by epinephrine (Alexander<sup>2</sup>).

Therefore, pertussis and bronchopneumonia can hardly be considered as forerunners of true bronchial asthma. There are no actual observations available which substantiate the claim that bacterial infection may develop into an allergic condition. Allergic asthma and allergic rhinitis are frequently misinterpreted, in the beginning, as respiratory infections; thus the history of patients with true bronchial asthma may reveal "colds" and the like as precursor conditions. Diagnostic errors of this type do not justify the tendency to concentrate on the search for allergens in an asthmatic patient, thereby disregarding preceding respiratory infections.<sup>57</sup> A pneumonia, years before the onset of the asthma, may at times explain the situation more adequately than allergy or suspected allergy to dust and certain foods.

The conception of a transition from extrinsic to intrinsic asthma appears also rather academic. In the few patients of this series in which simple allergy seemed to develop into a different and more serious disease, the relationship between acute infection and the following infectious asthma



proved to be the same as in cases without allergy. Rackemann came to similar conclusions in his study of intrinsic asthma.<sup>39</sup>

Since common allergic manifestations occur rather frequently among the whole population, their presence in asthmatic patients does not necessarily explain the etiology of the asthma. Coexisting allergy in patients with heart disease, tuberculosis, and especially in those who suffer from chronic, nonspecific respiratory infections undoubtedly complicates the situation in theoretical and practical respects. A reflex mechanism or bacterial allergy may, in these cases, be of some significance for the asthmatic symptoms, although it has been emphasized that hypersensitivity to bacterial proteins can be held responsible for asthma of the infectious type, at best, in only rare instances.<sup>23,45</sup> In the majority of chronic asthmatic patients without evidence of allergy, the direct action of bacterial agents should be considered as the cause of the disease. Bacteria have the capacity to produce lesions with spasm and exudation in bronchial structures, factors from which obstruction of the air passages and asthmatic symptoms may develop.

The life history of patients with infectious asthma is, as a rule, of greater diagnostic help than the eosinophil count and positive skin tests without clinical relationship. The questionable significance of these laboratory tests has become more and more evident in recent years.<sup>24,30,41,50</sup>

The therapeutic failure in most cases of infectious asthma is explainable since none of the usual treatments is primarily directed against the original pulmonary infection. The attempt to influence, by desensitization, the immunological processes which might be involved in the development of chronic pyogenic lesions in the respiratory system is no more rational than was tuberculin treatment for tuberculosis, years ago. Elimination of existing nose and sinus infection, alone, should not be expected to cure infectious asthma, since this condition originates from infections which frequently involve upper and lower respiratory system simultaneously.<sup>8,14</sup>

All deaths from asthma in this hospital during the past ten years occurred among the 100 patients with infectious asthma. Death was chiefly due to asphyxia caused by suppuration in the bronchopulmonary system. Whereas the deleterious action of opiates in certain cases of asthma has been generally attributed to nonspecific action on bronchial secretion, respiratory center and on cough reflex, the question is still open for discussion whether aspirin acts specifically on an allergic basis or by an unspecific mechanism. It is known that aspirin-sensitive patients belong, as a rule, to the severe, intractable group of intrinsic asthmatic patients who lack other clinical hypersensitivity (Van Leeuwen,<sup>59</sup> Rackemann<sup>42</sup>), as it was also found in this investigation.

It appears that generally accepted diagnostic criteria for death from asthma are as questionable as they are for asthma during life. Since excessive bronchorrhea may be responsible for the asphyctic deaths of pa-

tients with chronic bronchitis, silicosis, pneumonia and lung abscess, death in an "asthmatic attack" (Thieme, Sheldon<sup>53</sup>) does not indicate the nature of the asthma. Moreover, patients who die from asthma usually belong to the intrinsic type. Their life history has been in many cases characteristic of infectious asthma rather than of allergic asthma.<sup>12,20,23,32,42,53</sup>

In these patients, the pulmonary lesions are usually of that type which is commonly found in chronic nontuberculous infections of the lungs. Nevertheless, pulmonary suppuration, bronchiectasis and fibrosis, emphysema and atelectasis have been considered as pathological features of asthma if the patient presented asthmatic symptoms during life. The same can be said with regard to certain histological findings such as eosinophilic infiltration and hypertrophy of bronchial structures. Although they too may occur in a variety of conditions, especially of infectious nature, without asthmatic manifestations,<sup>27,53</sup> they are still considered as indicative of bronchial asthma. Actually, they are of little value in the pathological differential diagnosis between infectious and allergic asthma. Other histologic findings, such as sacculation of bronchi,<sup>13,53</sup> appear to be more significant because they strongly suggest an infectious process, even if reported in deaths from bronchial asthma without complications.<sup>58</sup> The presence of sticky material, plugging bronchi and bronchioles, has been considered as another characteristic feature of fatal asthma.<sup>42</sup> It needs hardly be mentioned that mucopurulent bronchial secretion, due to pyogenous infection, may also lead to plug formation and to death from asphyxia, with or without asthmatic symptoms.

It appears that the interpretation of all these pathologic changes as being complications of bronchial asthma is not warranted. In patients with infectious asthma, in which allergy seems to play no major part, the assumption that bronchiectasis and other lesions are due primarily to allergy confuses the true situation. It is appreciated that in certain instances allergy and other mechanisms besides infection may be responsible for pulmonary lesions.<sup>1,41</sup> This does not change the stand which has been taken here, and is supported by previous observations,<sup>20,23</sup> that bacterial infection as such is the direct cause of many cases which have been and still are considered as bronchial asthma, allergic bronchitis, and allergic bronchiectasis.

The conclusions to be drawn from this study in practical respect are obvious. Accepting an acute bronchopulmonary infection as the origin of infectious asthma, a rational therapy of this disease has to consider, most of all, its initial stage. The early elimination of the "focus of infection" in the lower respiratory system, by all therapeutic measures at our command, is the safest way to prevent its perpetuation, regardless of immunologic mechanisms possibly involved.

If, in the future, intelligent and conscientious consideration will be given to this problem, the high incidence of "chronic bronchitis" and of "infec-

tious asthma" will be avoided, and a great deal will be accomplished in the prevention of bronchiectasis.

## SUMMARY AND CONCLUSIONS

1. One hundred selected cases of infectious asthma have been studied as a group. The incidence, age, cause and clinical-pathological features of this condition have been correlated.

2. The analysis of this series and the findings of other comparable studies indicate that infectious asthma, under its various terms, is basically chronic bronchitis, the pathogenic factor being nonspecific, chronic, bronchopulmonary infection. The asthma in this condition is a symptom, and should be considered apart from allergic bronchial asthma. Allergic manifestations, which are present in certain cases of infectious asthma, are coincidental in character.

3. Rational therapy of infectious asthma must be directed toward the earliest possible elimination of the pulmonary infection itself from which the disease originates. All modern therapeutic measures should hereby be used, especially the sulfonamides and antibiotics. By these means, serious pulmonary diseases, such as bronchiectasis, may be prevented.

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# Department of Clinical Pathology and Laboratory Procedures

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## THE ETIOLOGY OF CHRONIC URTICARIA

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DURING the last fifteen years, as knowledge concerning the management of allergic diseases has become more widely disseminated among the general practitioners, the specialist in allergy has come to see fewer and fewer cases of simple, short-duration urticaria. Many of the obvious food cases are successfully managed by simple trial diets and, indeed, many patients have learned to solve their own problems without recourse to medical advice. The widespread use of the anti-histaminic drugs has likewise contributed its share to the control of the simple cases of urticaria. For some time now, the patients with urticaria whom we have seen are highly selected. The selected group includes those in whom simple trial diets and perhaps skin testing have been of no avail, those in whom symptoms have persisted for a number of months and sometimes years, and those in whom the anti-histaminic drugs have been without benefit.

In my opinion, based upon my experience with this group of cases, the most common etiologic factor is infection. Almost all of these patients will present some other definite evidence of a low-grade, chronic inflammatory reaction. This is especially true if blood count, sedimentation rate and Weltman coagulation tests are made. In almost every case one will find some evidence of an inflammatory response in the blood, either an elevated blood count, sedimentation rate or a Weltman shift indicating inflammation. Sometimes all three of these are abnormal. It then becomes a matter of searching out the location of the chronic infection by the usual and appropriate means. In other instances, routine examinations of the stools will reveal parasitosis. Occasionally, one encounters a patient with a definite decrease in prothrombin level in the blood, not associated with infection, on whom it is appropriate to try vitamin K therapy.

Without presenting a statistical analysis, I am sure that after adopting this viewpoint and approach in the chronic urticarias, that we relieve a good many more patients than were relieved in the past by the more conventional allergy approach. Within the past two years, two patients have been relieved of their chronic urticaria by treatment of gall-bladder infection. One has been relieved by the eradication of a dental infection. One has been relieved by appropriate therapy to a chronic prostatitis. Several have been relieved by penicillin or sulfadiazine therapy, or a combination

of the two, when no specific infection could be found yet when there was a definite indication of such infection on examination of the blood. Two have been relieved by clearing chronic urinary tract infection. One has been relieved by the eradication of giardia from the intestinal tract and gall bladder. Two with very low serum proteins, apparently the result of a too rigidly limited diet following previous skin testing of foods, were relieved by the simple expedient of placing them on a completely unlimited diet, with the assurance that they did not have a lifetime intractable allergic problem.

I make these few remarks to emphasize the plea for more careful diagnostic consideration of the chronic urticarial problem. It is my conviction that a careful diagnostic program is a great time saver. We are all too prone to be guided by a statistical consideration of large numbers of cases. One will readily admit that such cases are indeed a small percentage of the sum total of all urticarias, and we are therefore likely to leave such problems for consideration until everything else has failed. However, in the light of the individual patient the situation is exactly reversed. The patient's case is 100 per cent of those cases in which he is interested. The correct answer for his particular problem is his sole objective. We should therefore consider all possibilities for each case and not limit ourselves to the most frequent or simplest etiological explanation.

We feel that a more general use of laboratory aids will materially improve one's ability to detect the possibility of such etiologic factors.

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## THE SIGNIFICANCE OF CHRONIC BRONCHITIS IN INFECTIOUS BRONCHIAL ASTHMA

*(Continued from Page 375)*

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333 Park Avenue  
Rochester 7, New York.

JULY-AUGUST, 1947

## FALL GRADUATE INSTRUCTIONAL COURSE

This course is presented to provide a more comprehensive understanding of the many manifestations of allergy so commonly encountered by both the general practitioner and specialist and to emphasize methods of diagnosis and treatment of allergic diseases so that the physician is prepared to give the greatest aid to his patient.

*Monday, November 3, 1947*

### FUNDAMENTALS OF ALLERGY

- 8:30- 9:30 Registration.
- 9:30- 9:45 Address of Welcome, Dean Stanley Dorst.
- 9:45-10:30 "The Physiology of Allergy," Dr. Fred W. Wittich.
- 10:30-11:15 "Immunological Aspects of Allergy," Dr. Mary Loveless.
- 11:15-12:15 "The Clinical Significance of Recent Chemical Studies of Allergens," Dr. Harry S. Bernton.
- 12:15- 1:15 "Basic Principles of Allergy"—Moving Pictures, Dr. Bret Ratner.
- 2:15- 3:15 "Psychosomatic Factors in Allergy," Dr. John H. Mitchell.
- 3:15- 3:45 "Present Status of Antihistamine Drugs," Dr. Jonathan Forman.
- 3:45- 5:00 "Pharmacology of the More Important Drugs Used in Allergy," Dr. D. E. Jackson.
- 7:00 Informal Dinner—Speaker: Dr. Hal M. Davison.

*Tuesday, November 4, 1947*

### FUNDAMENTALS OF ALLERGY

- 9:00- 9:30 "X-Ray in Allergy; Diagnosis and Treatment," Dr. Paul Moore.
- 9:30-10:30 "Bacterial Allergy," Dr. E. E. Ecker.
- 10:30-11:15 "Food Allergy," Dr. Hal M. Davison.
- 11:15-11:45 "Balanced Diet," Dr. William B. Bean.
- 11:45-12:30 "Elimination Diet," Dr. Herbert J. Rinkel.
- 12:30- 1:15 "Physical Allergy," Dr. Harold A. Abramson.
- 2:15- 3:15 "The Preparation and Standardization of Extracts," Dr. Morris A. Kaplan.
- 3:15- 4:00 "Skin Testing: Technique and Interpretation," Dr. William F. Mitchell.
- 4:00- 4:30 "History Taking," Dr. J. Warrick Thomas.
- 4:30- 5:00 Demonstration, Dr. Charlotte Wiedemer.

*Wednesday, November 5, 1947*

### RESPIRATORY ALLERGY

- 9:00- 9:45 "Pathology of Asthma," Dr. Milton G. Bohrod.
- 9:45-11:15 "Bronchial Asthma: Diagnosis, Management and Treatment," Dr. Leon Unger.
- 11:15-12:00 "Aerosol Treatment of Asthma," Dr. Harold A. Abramson.
- 12:00-12:30 "Bronchoscopy in the Treatment of Asthma," Dr. Howard L. Stitt.
- 12:30- 1:15 "Cardiac Asthma and Cor Pulmonale," Dr. J. Harold Kotte.
- 2:15- 3:15 "Allergic Bronchitis, Bronchiectasis and Loeffler's Syndrome," Dr. Vincent J. Derbes.
- 3:15- 3:45 "Allergic Rhinitis," Dr. French K. Hansel.
- 3:45- 4:15 "Aural Allergy," Dr. Hugh A. Kuhn.
- 4:15- 5:00—"Ocular Allergy," Dr. A. D. Ruedemann.
- 8:00-10:00 Clinic.

## FALL GRADUATE INSTRUCTIONAL COURSE

*Thursday, November 6, 1947*

### HAY FEVER

- 9:00- 9:30 "Botany of Hay Fever Plants," Dr. Roger P. Wodehouse.  
9:30-11:00 "Hay Fever: Diagnosis, Treatment and Management,"  
Dr. George E. Rockwell.  
11:00-11:45 "Pollen Respiratory Allergy with Negative Cutaneous Reactions,"  
Dr. M. Murray Peshkin.  
11:45-12:45 "Mold Allergy: Symptoms, Diagnosis and Treatment,"  
Dr. Homer E. Prince.  
12:45- 1:15 "Pollen Counts and Demonstration," Dr. Charlotte Wiedemer.  
2:15- 3:15 "Vascular Allergy," Dr. Milton G. Bohrod.  
3:15- 5:00 "Clinical Use of Histamine," Dr. Bayard T. Horton.

*Friday, November 7, 1947*

### DERMATOLOGIC ALLERGY

- 9:00- 9:45 "Atopic Dermatitis," Dr. Stephan Epstein.  
9:45-10:45 "Contact Dermatitis," Dr. Leon Goldman.  
10:45-11:25 "Urticaria," Dr. R. F. Hughes.  
11:25-12:20 "Soap and Other Detergents," Dr. Irvin H. Blank.  
12:20- 1:30 "Drug Allergies," Dr. Ethan Allan Brown.  
2:30- 3:00 "Joint Allergy," Dr. Bela Schick.  
3:00- 4:15 "Neuro Allergy including Migraine," Dr. Foster Kennedy.  
4:15- 5:00 "Unusual and Obscure Conditions of Allergies," Dr. C. R. K. Johnston.

*Saturday, November 8, 1947*

### PEDIATRIC ALLERGY

- 9:00- 9:45 "Management of the Pre-Allergic Child," Dr. Bret Ratner.  
9:45-10:30 "Characteristics of the Allergic Child," Dr. A. B. Schwartz.  
10:30-11:45 "Special Problems in Treatment and Management of Asthma in Children," Dr. George Piness.  
11:45-12:45 "Infantile Eczema," Dr. Albert V. Stoesser.  
12:45- 1:30 "Gastro-intestinal Allergy in Children," Dr. Orval R. Withers.

On Tuesday, Thursday and Friday evenings from 8:00-10:00 p.m., there will be instructors in Parlors A and B, Netherland Plaza Hotel, so that students may visit, ask questions and have informal discussions.

Speaker at Large and Director of Round Table Discussion, Dr. George L. Waldbott.

Make all reservations for the Course and hotel accommodations directly with the secretary, Dr. Fred W. Wittich, 423 La Salle Medical Building, Minneapolis, Minnesota. When requesting your reservation, please state the exact time of your arrival and departure and whether you want a single room or wish to share one with another registrant. The number of single rooms is limited. The fee for the Course is \$100.

JULY-AUGUST, 1947



# Editorial

*The opinions expressed by the writers of editorials in the ANNALS are individual and do not necessarily represent the group opinion of the Board or of the College.*

## HORSE IMMUNOLOGY FOR ALLERGISTS

Allergists and immunologists share to a large extent the problems of theoretical conception and of experimental approach. A series of papers from Heidelberger's<sup>1</sup> laboratory concerning the immune response of the horse, just published, merits a word of comment here, because it sheds light on three aspects of immune reactions, of which—we suspect—our readers are not always aware: namely, the multiplicity of antibodies, the occurrence of non-precipitating antibodies, and the influence of the site or mode of introducing antigens upon the immune response.

Two kinds of precipitating (and protecting) antibodies are known to be formed by the horse. One is typically represented by the antitoxins. They are water soluble and give the characteristic prozone effect of the toxin-antitoxin flocculation. The other is typified by the antibodies versus the carbohydrate antigens of bacteria as, for instance, of pneumococci. They are water-insoluble and do not give prozone effects.

In one of Heidelberger's horses, that on a previous intravenous immunization with rabbit globulin produced precipitating antibody, a series of intradermal and subcutaneous injections with the same antigen evoked a non-precipitating antibody. Similar observations have been recorded before—first by Coca and Kelly<sup>2</sup> in rabbit sera versus *H. influenzae*. Antibodies can be traced *in vitro* either by the inhibition of the reaction of "normal" antibody or by the demonstration of the addition of nitrogenous matter to corpuscular antigen after contact with the serum. Recently, non-precipitating antibodies have also been found in man: namely, in anti-Rh sera<sup>3</sup> and in sera versus Shiga and typhoid bacilli.<sup>4</sup> It is perhaps permissible to hope that the study of these antibodies will help in the understanding of the differences between "allergic" and "immune" mechanisms.

It is an old experience that antitoxin production in horses depends greatly on the route of immunization; on subcutaneous injections abundant antitoxin is formed; intravenous injection is not successful. Heidelberger noted similar differences in the response to his proteinic antigens: anti- (rabbit-) albumin antibodies of the antitoxin type were freely produced only upon subcutaneous and not after intravenous introduction of the antigen. However, the precipitin type of antibody versus rabbit

*(Continued on Page 396)*

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2. Coca, A. F., and Kelly, M. F.: *J. Immunol.*, 6:87, 1921.
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# Progress in Allergy

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## RESPIRATION

### A Review of Recent Literature

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The textbooks concerned with the subjects of bronchial asthma take for granted, in their readers, a knowledge of the mechanism of normal and abnormal respiration. Since the advances in this field have been many during the last decade, a partial review of the subject would seem to be necessary, especially since the facts now known will not be part of medical literature for some years. The present paper is concerned with some of the more important discoveries, and especially those of which knowledge is necessary for the full understanding of conditions treated by the internist specializing in allergy.

For the anatomy of the lung, the classical monograph by Miller<sup>43</sup> is required reading. For the physiology, it would be difficult to improve upon Wright.<sup>58</sup> For general analysis, reference must be made to Gray<sup>29</sup> or to Richards.<sup>51-53</sup> Since all of the work of recent years on respiration cannot possibly be reviewed, a bibliography listing the more important papers by Alexander and Kountz,<sup>1</sup> Anthony,<sup>2,3</sup> Barach,<sup>4,5</sup> Christie,<sup>10-13</sup> Cournand,<sup>14-18</sup> Hermannsen,<sup>33</sup> Hurtado,<sup>34,35</sup> Knipping,<sup>37</sup> and Kountz,<sup>38,39</sup> will be found at the end of this paper.

Respiration, undoubtedly one of the most complex of the body functions,<sup>27</sup> is controlled by a number of factors, the immediate being the bilateral intracranial centers in the medulla and the bilateral extracranial carotid sinus mechanisms at the bifurcation of the carotid arteries. The distant controls include the higher centers and their hidden and overt effects as well as the tissue enzymes. The intermediate controls are placed in the cardiac and the vasomotor centers, the aortic arch, the lung itself, as well as the chest wall. The multiple factors involved form an intricate complex of physical, chemical, and neuromuscular stimuli associated with systems as diverse as the excess or lack of either carbon dioxide or oxygen, the rise or fall of the blood pressure, the metabolic rate, the composition and reaction of the blood, and the presence or absence of the respiratory enzymes. If to this incomplete list we add the effects of anatomical or pathological abnormalities, acute or chronic infections, neoplasm, congestion or collapse, and allergic sensitivity, all of which reflectly may stimulate or depress respiration, the problem becomes complex indeed.

To begin with the individual cell, respiration is a cycle in which molecular oxygen reacts with bivalent iron, which, oxidized in turn, reacts with the tissues and is again reduced to bivalent iron. This process occurs on the surface of the cell and as such may be inhibited by substances such as narcotics, which, themselves incapable of being used in this manner, crowd the material to be oxidized away from the surface. The process, too sluggish for practical purposes, must be mediated by enzyme activity; that is, by respiratory ferments. Of these, if we limit ourselves to internal respiration, we have Keilin's Cytochrome C and Warburg's yellow enzyme,<sup>56,57</sup> now known to represent five enzymes; flavoproteins of which the pigment portion consists of the phosphoric acid ester of riboflavin.<sup>7</sup> Not only does the acceptance of oxygen require enzymatic activity, but the release of carbon dioxide is also accelerated by an intracellular enzyme, carbonic anhydrase affecting carbaemoglobin.<sup>54</sup> This knowledge may appear purely theoretical and relatively un-

important, except for recent work which demonstrates the changes which may occur following the injection of Cytochrome C into the body.

Proger and his colleagues,<sup>48-50</sup> as a result of being able to demonstrate that the Cytochrome C content of the heart, brain, liver, and kidney might be far below that required for the maximal activity of the Cytochrome oxidase present, injected the material intravenously and demonstrated that it was stored in these organs and produced a significant increase in the tissue uptake of oxygen. Under conditions of severe anoxia (3 per cent oxygen and 97 per cent nitrogen) there was a striking increase in survival time in rats, previously injected with Cytochrome C, as compared with control animals. It was then demonstrated that the extreme subjective disturbances, which occasionally occur with anoxia, induced by a mixture of oxygen (10 per cent) and nitrogen (90 per cent) could be prevented by the injection of 25 to 30 mg. of Cytochrome C. Electrocardiogram changes were also demonstrable. In intermittent claudication, seven of thirteen patients showed striking improvement; three, moderate effects; and three, no effect, the increased exercise tolerance continuing for almost one year after the last injection. During an initial control period following the injection of an inert solution for eight days, there were no effects.

Our own experience<sup>8</sup> with patients suffering from dyspnea associated with extreme emphysema corroborates the salubrious effects of Cytochrome C injection.

The intermediate mechanisms can be discussed in turn, and then correlated since none acts independently of the others. The excess of carbon dioxide is affected by, and will affect, the reaction of the blood, the aortic body of the aortic arch, the carotid body, and also the respiratory center, and will increase first the depth and then the frequency of respiration. Since the H-ion concentration of the blood is diminished during gastric secretion, bicarbonate ingestion, or an alkaline-ash diet, all three factors will depress respiration until the tendency toward alkalaemia has been compensated.

Conversely, during intestinal digestion, ammonium chloride ingestion and acid-ash diets, as well as in diabetes and starvation, respiration is stimulated until the tendency toward acidemia has been checked. It should be noted that both of these descriptions are over-simplified and neither is completely true. As stated by Gray,<sup>20</sup> if test subjects are made to breathe varying percentages of carbon dioxide under conditions of rest, exercise, anoxia, and ammonium chloride acidosis, the result curves are linear and with similar slopes but differing positions. Since the constancy of the slope of the curve indicates that a given increment of stimulation produces the same increment in response, independently of the conditions, this must be taken as evidence of unaltered irritability suggesting the influence of an additional factor.

The effects of oxygen lack depend upon whether they are gradual or sudden in onset. When they are slow, as seen in changes of altitude, no symptoms occur until a height of approximately 12,000 feet is reached, at which point the increase occurs in rate and not in depth of respiration, the increased pulmonary ventilation washing out the carbon dioxide, and depressing respiration. The successive stages of this cycle take place as follows: The oxygen lack stimulates respiration, which increases pulmonary ventilation, resulting in lowered alveolar carbon dioxide, which in turn lowers arterial oxygen and causes alkalaemia, depresses respiration until the carbon dioxide tension increases, or the oxygen lack is again felt. Unfortunately, oxygen lack greatly depresses the isolated respiratory center, and if the vagi and sinus nerves are severed, the same mixture rapidly causes respiratory paralysis. In the intact subject, therefore, oxygen lack acts chiefly upon the chemo-receptors of the aortic arch and carotid sinuses<sup>20</sup> and so reflexly stimulates increased respiration. The respiratory center appears to be much more sensitive to carbon dioxide excess alone than to carbon dioxide excess combined with oxygen lack.

The actions of oxygen excess must be mentioned since they are not as generally

appreciated as are the effects of carbon dioxide excess. Mixtures containing oxygen (60 per cent) can be breathed indefinitely and cause no change in pulmonary ventilation, metabolic rate, blood pressure, or mental activity. Animals exposed to mixtures containing oxygen (75 per cent) develop pulmonary congestion and consolidation and die within a few days. Animals exposed to pure oxygen at several atmospheres pressure, develop coma and die rapidly. Men exposed to pure oxygen at four atmospheres develop a fall in blood pressure, convulsions, and faintness within an hour. The poisonous effects are due in part to the retention of oxygen. The oxygen dissolved in plasma normally totals 0.3 per cent. In pure oxygen, at a pressure of one atmosphere, this dissolved oxygen increases to 2 per cent, sufficient to meet the resulting oxygen requirements in the tissues which are about 3 c.c. per 100 c.c. of blood flow. Since the oxyhaemoglobin is not reduced, no carbohaemoglobin can be formed and the carbon dioxide is therefore retained in the tissues in toxic amounts.

The respiration of pure oxygen can be used to measure the effectiveness of aeration of the pulmonary system. The index known as the pulmonary emptying rate is attained by having the subjects breathe pure oxygen for seven minutes. The percentage of nitrogen which remains in the alveolar air is a significant factor, and in normal subjects is less than 2.5 per cent while in emphysematous conditions, the index may be over five per cent. The relation between the minute pulmonary ventilation and the amount of oxygen absorbed, expressed as the difference in per cent concentration of oxygen between inspired and expired air, is termed the oxygen utilization co-efficient. Anthony<sup>2,3</sup> has taken the reciprocal of pulmonary ventilation/oxygen consumption as the ventilatory co-efficient. In normal individuals, the co-efficient of oxygen utilization varies from 4.5 to 5.5 per cent, with an increase of 0.5 per cent for mild or moderate exercise. In bronchial asthma, the patient breathes a much larger volume of air for a given oxygen absorption and the oxygen utilization decreases occasionally as low as 3.0 to 3.5 per cent.

At this point, the effect of hyperventilation, often seen in emotional patients subject to bronchial asthma, should be reviewed.

Apropos of the antiquity of the descriptions of the hyperventilation syndrome is a passage taken from DuLaurens in 1559<sup>19</sup> who says, "Melancholoke folke are commonly given to sigh because the minde being possessed of great varietie and store of foolish apparitions, doth not remember or suffer the partie to be at leisure to breathe according to the necessitie of nature, whereupon she is constrained at once to sup up as much aire as otherwise would serve for two or three time; and this great draught of breath is called by name sighing, which, as it were, a reduplicating of the ordinary manner of breathing. In this order it falleth out with lovers, and all those who are very busily occupied in some deep contemplation. Sillie fooles likewise, fall into wonder at the sight of any beautiful and goodly picture are constrained to give a great sigh, their will (which is the efficient cause of breathing) being altogether distracted and wholly possessed with the sight of the image."

Two or three minutes of voluntary hyperpnoea will be followed by a period of apnoea, and then by a phase of periodic breathing. If continued for longer than a few minutes, the over-ventilation causes a leukocytosis, hyperglycemia and a diuresis, with acetone bodies. The lowered carbon dioxide tension acts directly upon the arterioles of the skin, which becomes white and cold. There is undoubtedly a relationship to epinephrine absorption and effect if the medication is injected for a concomitant wheezing. If the subject takes pure oxygen and carbon dioxide (5 per cent) during a period of hyperventilation, no ill effects occur. If pure oxygen is taken alone, apnoea, which may last up to eight minutes, appears, and respiration then recommences of itself.

That the act of forced hyperventilation should cause many primary and secondary effects upon the cardiovascular and nervous systems should not surprise us. As

Mills<sup>44</sup> said, "The primary phenomenon may be considered as a powerful, neuronie discharge, whose precise distribution is entirely unknown, but which greatly increases the respiratory movements. The consequent over-ventilation of the lungs, the altered chemical composition of the blood; and the muscular movements involved in breathing produce large rhythmic fluctuations in intra-thoracic and intra-abdominal pressures, which, we can agree, affect the circulation of the blood. The chemical changes may directly affect the activity of different levels of the central nervous system, and also by direct or reflex action on the heart and vascular calibres, produce alterations in the circulation; and such alterations in the circulation, produced directly or indirectly, may alter blood flow through parts of the central nervous system and hence produce chemical changes there." In discussing the phenomenon that the hypernoea may continue, he goes on to say that, "An increased venous return induced particularly by diaphragmatic over-ventilation may be the cause of such continued dyspnea, the hypernoea being decreased or absent if the venous return is limited by the occlusion of blood in the lower limbs. Some subjects are persistently hypernoeic after forced breathing, whatever measures are taken to exclude, diminish, or increase the possible modes of stimulation of the respiratory center. The latter type of hypernoea is independent of apnoea and the giving of an alveolar sample, and quite uncorrelated with blood pressure changes; it is undiminished when the venous return is restricted by occlusion of the blood in the lower limbs; it is uncorrelated with modifications of electrical activity of the cerebral cortex induced by forced breathing. It is therefore suggested in part by exclusion and in part through some positive lines of evidence that it results directly from that same cortical activity which is initially responsible for the forced breathing."

The nervous pathways involved are three, all of which merit brief review.

The action currents of the single fibres of the phrenic and intercostal nerves and of single motor units of the muscles involved demonstrate that during respiration at rest, the muscles are being stimulated subtetanically, the impulses reaching them at a rate of 25 per second. The discharge is asynchronous, the motor units out of phase, and since only a proportion of the fibres are stimulated, the muscle pull is steady. For deep respiration, the impulse discharge rate reaches as high as 100 each second, affecting large numbers of motor units at a more synchronous rate, causing full tetanus and more forceful contraction of the diaphragm and the external intercostal muscles. Direct recording of the electrical changes in the intercostal muscles demonstrates active contraction of the expiratory muscles during the expiratory phase of deep respiration.<sup>22</sup>

A second set of impulses, inhibitory in nature, proceed, during inflation from the pulmonary tissues along the vagus to the respiratory center, eventually causing inhibition of inspiration, while during expiration, a corresponding set of fibres send increasing stimulating impulses, eventually causing the cessation of expiration and the initiation of inspiration. This effect, the Hering-Breuer reflex,<sup>32</sup> will not occur if both vagi are severed, respiration then remaining a series of slow, deep inspirations and expirations.

A third set of impulses arises in the smooth muscle fibres of the bronchi, which receive fibres from the sympathetic system, affecting dilatation, and from the vagi, affecting constriction. The afferent impulses in the vagus reflex controlling asthma may arise not only from the nose (Brodie-Dixon reflex), the irritation of non-specific irritations, but also from non-passive expiration as in chronic cough, and from the local effects following allergen inhalation or histamine release, due to local infection as well as to blood stream changes following the ingestion or injection of allergens.

The nerve pathways for the Brodie-Dixon reflex described above have been studied and there is much experimental and factual evidence to support the view

that an abnormal nasal condition can, when the "soil" is suitable, give rise to reflex bronchial asthma. Myers<sup>45</sup> has shown by micro-dissection that the pathways for the reflex probably pass through the anterior ethmoidal nerve, the first division of the fifth (trigeminal) nerve, the gasserian ganglion, and the nucleus of the fifth nerve in the upper part of the pons. From here, the fibres can be traced to the nucleus ambiguus in the medulla. Here the vagus and glossopharyngeal nerves originate. Other fibres from the nose pass through the sphenopalatine ganglion to reach the nucleus of the vagus. In patients in whom this reflex is thought to operate, the spraying of the nasal mucosa with a cocaine solution (2 per cent) should afford almost immediate, although transient, relief from the wheezing.

Our own work corroborates such effects occasionally strikingly dramatic in patients with status asthmaticus. Sensitivity to cocaine must of course be excluded. As a clinical example in this regard, Shields<sup>55</sup> describes a patient with left-side trigeminal neuralgia and bronchial asthma, who, following the division of the sensory route of the gasserian ganglion abolished the attacks of bronchial spasm in the left lung, while typical signs of bronchial asthma persisted on the right side.

Since the aeration of the blood in the lesser circulation depends on its quantity in the pulmonary bed, it should not surprise us to discover that an additional mechanism mediated by another set of reflexes operates in this area. This pulmonary hemodynamic mechanism has been described by Parin,<sup>46</sup> who, by a most ingenious set of experiments, revealed that a rise in pressure within the vessels of the isolated lung was always accompanied by a fall in pressure in the systemic arterial bed, and in most cases, by a slowing of the heart rate. It required only a slight rise in pulmonary pressure to produce a very measurable decline in arterial pressure, the two being proportional and associated with a slowing of the heart beat. The receptors of these reflexes, probably located in the arteries or veins of the lesser circulation, act in two ways: first, to protect the weaker muscles of the right heart from overwork by lowering the cardiac capacity and producing vasodilatation with a fall in systemic blood pressure; and, second, to increase the capacity of blood reservoirs whenever the pulmonary circulation is taxed. Its second function acts undoubtedly to prevent pulmonary edema.

That the pulmonary arteries and veins not only protect the heart but also act as an "accessory heart" can be concluded from the work of Mac Klin,<sup>41</sup> who shows that the vessels are surrounded by expanding and contracting air spaces, which causes a rhythmic increase and decrease in their calibre with each respiratory cycle. In inspiration, the vessels become elongated and widened by the traction of the fibres connecting their walls with the enveloping air spaces. In expiration, they are shortened and narrowed by the recoil of their specialized elastic fibres. In inspiration, therefore, their blood content is increased and in expiration, decreased. The heart responds to the advantage of enlarged vascular capacity by beating faster and increasing its output into the pulmonary vascular bed, which is therefore a bridge for the blood, which must flow in sufficient amounts if systemic vessels are to be supplied properly. This ability on the part of the lesser circulation to adapt itself to the demands of long and continuous physical exercise is directly due to the distensibility and contractibility of these vessels as due to the expansion and contraction of the air sacs and the function of "accessory heart" taken on by the vascular bed.

An interesting correlation not generally known because sympathectomy is performed uncommonly for the treatment of bronchial asthma in this country, is suggested by the work of Hagen.<sup>31</sup> In seven patients, for whom the cervical ganglion had been removed surgically for the treatment of bronchial asthma, the sections of these ganglions showed the majority of the ganglion cells to present pathological changes.

Vacuolation and granular degeneration are seen in the body of the ganglion and

spherical terminal formations in the processes point to the presence of pathological irritation. There is accumulation of pigment, as well as nuclear changes in the cells. The author feels that increased appearance of multinuclear ganglion cells and the pathological changes observable in them represent another degenerative process in bronchial asthma. He feels that the microscopic changes indicate not only that bronchial asthma is a "functional" disorder, but that serious organic changes co-exist in the sympathetic nervous system, and that these changes in the sympathetic cervical ganglion are the causes of the secondary symptoms of asthma. Such disturbances in the development of the sympathetic system may be decisive in the constitution of the asthmatic patient and may precede the asthma, be caused by it, and perhaps directly cause it in a reciprocal relationship.

The adaptations due to exercise are capable of simple review.<sup>47</sup> The pulmonary ventilation is increased by emotional tension, by the increase of carbon dioxide in the blood, by the rise in body temperature due to the additional metabolism, and reflexly from the engorged right side of the heart. Unless the blood pressure is raised or lowered rapidly, it has no immediate noticeable effect upon the mechanism of respiration. Other factors of less importance are those caused by pain, thermal stimuli, swallowing and also sleep, during which respiration is usually depressed and alveolar carbon dioxide usually considerably higher than during waking periods.

For the evaluation of the role of the psychological factors in respiration, there are a number of reviews which vary from the purely psychoanalytical to the most objective type of laboratory test. The effects of emotion upon the movements of the diaphragm have been described as seen fluoroscopically by Faulkner.<sup>23,25</sup> While responding to questions evoking unpleasant states, the diaphragmatic excursions were constantly limited to one-half inch; while responding to pleasant mental pictures, the range of respiratory diaphragmatic movement extended to three and one-half inches, during a time that the patient was not conscious that he was being examined fluoroscopically for this purpose. These same patients had an associated cardiospasm. Faulkner has also demonstrated the influence of suggestion on the size of the bronchial lumen. During bronchoscopy, conversation about indifferent subjects caused no changes in the lumen of the bronchioles, while thoughts of insecurity and frustration caused spasm and a narrowed lumen, while suggestions of pleasurable nature caused bronchial relaxation. In a second patient, the spasm was associated with dyspnea, choking and wheezing. The psycho-biological aspects of respiration have been discussed by Binger,<sup>6</sup> who stresses the dyspnea associated with anxiety states, and also by Christie,<sup>10-13</sup> who contrasts the patients with anxiety neuroses, who present an irregular shallow type of respiration with the patients who present conversation hysterias and have a tendency toward hyperventilation. The relationships between anxiety states and hyperventilation have been discussed in detail by Kerr,<sup>36</sup> in one of whose patients 90 seconds of hyperventilation would cause an asthmatic attack.

The mechanism of cough is so closely related to that of respiration and to the chief presenting symptoms of so many of our asthma patients, that it, too, should be discussed.

Fenichel<sup>26</sup> in his analysis of the psycho-pathology of coughing lists six types of reactions. He points out that the severe organic cough of chronic states leads to an introversion. An intolerant patient with a chronic cough tends to become irritable, restless, angry, and accusatory of others. In the second type of patient, the cough becomes a substitution vent for relieving an inner pressure caused by repressions. In the third type of patient, whose respiratory tract has acquired a particular sensitivity to psychic stimuli, a cough may be imitated or a repetition due to an earlier experience in which coughing occurred. A fourth type is a psychogenic cough related to the "tics" as seen in a nervous person who does not wish to speak, and occasionally in audiences who do not wish to hear. The fifth type is

the cough, organic in origin but psychogenic in its persistence; and lastly, a type in which combined effects may be noted.

The internist, who sees patients with chronic bronchial asthma and emphysema, must have a clear picture of the respiratory readjustments which occur in his condition. The loss of elasticity of the lung tissues leads to a distension and a marked increase in the volume of the functional residual air. In normal individuals, this ranges from 35 to 40 per cent, but in emphysema may be as great as 70 to 80 per cent. The vital capacity is therefore reduced, and although at rest it may be quite similar to the normal, on exertion, the volume cannot be properly increased and respiration is shallow and rapid. In the more severe type of case, the resting tidal air and the vital capacity may approximate equality.

Meakins,<sup>42</sup> in his discussion on emphysema, shows how, with the loss of pulmonary elasticity, the natural elastic recoil of the lungs is absent, and the lung tissue must be compressed by an active expiratory effort with the generation of a positive intrapleural pressure, to which the thoracic cage in man is wholly unsuited. The diaphragm is a muscle of inspiration, and has not been constructed to resist an increase in intra-thoracic pressure which is bound to displace it downward with an impairment of its tone and contractile range. The displacement of the diaphragm can be prevented only by contraction of the muscles of the abdominal wall. The abdomen is often relaxed and pendulous in these patients and cannot therefore be used as an accessory aid to respiration. The over-voluminous contents of the thorax do not permit the diaphragm to rise to its normal position at the end of expiration. The alveoli, therefore, are not equally ventilated, since the superficial alveoli are distended, ischemic and relatively functionless, but over-ventilated at the expense of the deeper, healthier alveoli, which are under-ventilated.

Slowly, but inevitably, circulatory readjustments take place. The small but definite pressure gradient between the vena cava and the right auricle is governed by the negative intra-thoracic or intra-pleural pressure. As this becomes positive, an increase in the venous pressure takes place, which, in turn, progresses to congestive failure. Inspiration is altered because the muscles are in the inspiratory position. The air inspired is wasted on the peripheral functionless alveoli. The lungs cannot relax passively, except as a result of unnatural, expiratory effort. The imperfect aeration of the blood makes increasing demands for hyperventilation coupled with decreasing ability to ventilate.

Goggio<sup>28</sup> emphasizes the fact that there are two types of emphysema; the first, the postural or senile type, which occurs more frequently but is seldom of clinical significance; and the second, chronic, hypertrophic, or obstructive type, which has a younger age incidence, and in which the chief etiological factor is respiratory obstruction. Christie<sup>10-13</sup> states that in his experience, more than 90 per cent of the patients with the chronic hypertrophic type of emphysema give a significant history of asthma and chronic bronchitis. In one of the cases described by Goggio,<sup>28</sup> a patient with emphysema and an apparently normal vital capacity required twenty seconds to exhale the same amount of air as was exhaled by a normal subject in one and one-half seconds with ease, during which time the normal subject could expire 4 liters of air, while the patient could only expire 900 c.c. Goggio stresses the fact that, although the patient, on physical examination, may give no indication of any infective process in the lungs or of any asthmatic state, yet a careful history may reveal a formidable pulmonary infective prologue and may disclose indications of a possible bronchospastic factor. Among these, may be the paroxysmal nature of the dyspnea, its precipitation by emotion, the occasional presence of expiratory squeaks and groans, and the relief of the dyspnea for several months after an attack of pneumococcal pneumonia. The actual presence of the bronchospastic factor can be easily demonstrated when, immediately after physical examination has confirmed the absence of adventitious sounds in the chest, the administration



of a few minims of 1:100 epinephrine by nebulization results in a rise of vital capacity from 1,500 to 3,000 c.c. in 7 minutes. It is well to remember that marked bronchospasm can exist in the complete absence of adventitious sounds in the chest, and that the effect of epinephrine can be measured objectively for both diagnostic and therapeutic purposes.

Studies of oxygen saturation value in these emphysematous patients showed that it may be as low as 60 per cent, which corresponds to what might occur in an unacclimatized person at an altitude of 22,000 feet, a level at which mountain sickness occurs. The symptoms, therefore, of headache, dizziness, loss of appetite, weakness, fatigue, insomnia, tremor, tachycardia, and cyanosis, and occasionally episodes of disorientation, which occur in such patients, may be symptoms of mountain sickness and can be attributed to the attendant anoxia. The patients are relieved by oxygen therapy and the condition can be mitigated to some degree by an increase in the oxygen-carrying power of the blood. This mechanism may indeed explain our own success with the use of Cytochrome C in the emphysematous patients with dyspnea.

In some of the patients, who present a lowered vital capacity and dyspnea with no attendant pulmonary disease, the effect of pollen and other inhalants must be ruled out. In our own series, a group of patients with hay fever but with no clinical bronchial asthma presented this clinical syndrome.<sup>9</sup>

Advantage can be taken of some of these factors to distinguish between pulmonary and cardiac disease. Since forced expiration is a result of a muscular effort in which all the expiratory muscles normally participate, the vital capacity may be decreased through muscular insufficiency, although no abnormalities of circulation or of respiration exist. This muscular factor plays an important part in the diminution of the vital capacity caused by cardiac disease. It is important first to have a measurement of the patient's vital capacity taken standing, the highest readings being accepted. After a rest, the minimum duration of maximum expiration is measured by having the patient exhale as rapidly as possible following as deep an inspiration as he is capable of taking. The duration of the timed expiration is measured by stop-watch. After the vital capacity and the minimum duration of the quickest possible exhalation of the volume equal to the vital capacity has been measured simultaneously, the velocity of the spirometric respiration is obtained by dividing the vital capacity by the expiration time. The velocity of spirometric respiration is that air volume which enters the spirometer per second, representing the average of the quickest possible expiration.

It is indeed true that there is no relationship between the vital capacity (volume) and the expiratory pressure (strength), but the velocity of spirometric respiration depends on the vital capacity as well as on the expiratory pressure. Any decrease in vital capacity, due to cardiac disease, is characterized by prolongation of the expiration time, a decrease in the velocity of spirometric expiration, and, above all, by a decrease in the expiratory pressure, which in typical cases, is less than 50 per cent of the standard value. Decreases in vital capacity due to pulmonary disease are characterized by a greater prolongation of expiration time by distinct decrease in velocity of respiration and most of all by the fact that the expiratory pressure is normal or altered little if at all. The values obtained for normal individuals can be taken from the investigations by Gross,<sup>30</sup> who furnishes a table as a result of his studies.

Of interest to those who treat asthmatic patients are the comments of Eichler,<sup>21</sup> who found a tremendous, although transitory, increase in the histamine content of the blood plasma in cats breathing 10 per cent oxygen (equivalent to 18,000 feet), the circulation showing a rise from the normal of 0.056 to 0.12 to levels as high as 480 micrograms in the first 10 minutes, with a maintenance of such high levels for as long as one hour. Although the author does not suggest it, it may be possible that, due to lack of respiratory enzymes, or to oxygen absorption, similar lowered

oxygen tension may occur in asthmatic patients with severe emphysema and explain the effects of antihistaminic agents in some subjects and not in others.

It may be concluded from this brief review that respiration is a complex biological mechanism, stimulated, depressed and affected by many varied and diverse factors, no one of which operates alone. This multiple factor theory of the causation of respiratory ventilation is discussed in detail by Gray,<sup>29</sup> who states that while a number of factors exert independent effects upon respiratory ventilation, they are also mutually inter-dependent, so that a change in any one factor usually brings about changes in one or more of the other factors, the actual ventilation being defined as the algebraic sum of the partial effects of the separate agents. Since these lend themselves to mathematical description, it is possible to reduce them to working formulae. For those who wish to investigate these problems in the field of allergy, the four equations taken from this paper are listed. The symbols used have the following significance:

$pO_2$ —alveolar or arterial tension of  $O_2$

$pCO_2$ —alveolar or arterial tension of  $CO_2$

$FO_2$ —volumetric fraction of  $O_2$  in dry, inspired air.

$FCO_2$ —volumetric fraction of  $CO_2$  in dry, inspired air.

$H$ — $H$  ion concentration of arterial plasma.

$VR$ —alveolar ventilation ratio.

$VRpO_2VRpCO_2$ ,  $VRH$ —alveolar ventilation ratio as influenced by the definition of the subscript.

$VRr$ —partial ventilation ratio due to the action of muscular reflexes.

$MRR$ —metabolic rate ratio.

$B$ —barometric pressure.

$RQ$ —alveolar respiratory quotient.

$O_2$ —oxygen content of the blood in volumes per cent.

$O_{2150}$ —oxygen capacity of the blood in volumes per cent expressed as oxygen content of blood exposed to  $pO_2$  of 150 mm. Hg.

$BHCO_37.41$ —Bicarbonate content of volumes per cent of plasma from oxygenated blood at pH 7.41.

TABLE I. EQUATIONS AND MATHEMATICAL SYMBOLS

1. The general alveolar equation (relationship between  $pO_2$  and  $pCO_2$ )

$$pO_2 = \frac{(B-47-pCO_2)(RQ \cdot FO_2 + FCO_2) - pCO_2(1-FO_2)(1-RQ)}{RQ + FCO_2(1-RQ)}$$

2. The general ventilation equation (relationships between actual ventilation and  $pCO_2$ ):

$$\frac{47 MRR(RQ + FCO_2(1-RQ))}{pCO_2 - (B-47) FCO_2}$$

3. The general respiratory pathway equation (relationships between  $H$ -ion and  $pCO_2$ ):

$$PCO = \frac{H}{53.3} (16 + 2.3 O_{2150}) + \frac{(\log H - 1.59)}{BHCO_{37.41}} + 0.375 (O_{2150} - O_2)$$

4. The chemical ventilation equation (giving the sum of the partial effects of  $H$ -ion,  $pO_2$ , and  $pCO_2$  on ventilation):

$$VR = 0.22H + 0.262 pCO_2 + 18.0 + \frac{105}{10^{0.723 pO_2}}$$

## PROGRESS IN ALLERGY

To use a paraphrase of Gray's own words in explaining the derivation of the formulae, "The first step consisted of the derivation on formal grounds of what has been called the alveolar equation, which defines all possible relationships between alveolar  $O_2$  and  $CO_2$  tensions for any barometric pressure, alveolar  $RQ$ , and for any inspired gas mixture.

The second step consisted of an analogous derivation on formal grounds of what has been termed the formal ventilation equation, which defines the possible relationships between the actual ventilation and the alveolar  $CO_2$  tension for any condition of metabolic rate, alveolar  $RQ$ , and inspired gas mixtures.

The third step consisted of developing on empirical grounds what has been called the respiratory pathway equation, which defines the possible relationships between the arterial  $H$ -ion concentration and  $CO_2$  tension, for any conditions of bicarbonate capacity,  $O_2$  capacity, and arterial  $O_2$  saturation.

The fourth step to be completed consists of the isolation and quantification of the partial effects on ventilation of the three important chemical agents,  $H$ -ion,  $pCO_2$ , and  $pO_2$ .

One of the major achievements of the present theory is that it resolves the most persistent and controversial question in the field of respiration: "Should  $H$ -ion or  $CO_2$  be considered the true respiratory stimulus? From the standpoint of the multiple factor theory this question should be framed as follows: To what extent does each of the two agents influence ventilation? Equation 4, which accurately describes the extensive experimental data, provides a quantitative answer to this question. If it were true that only one of the two agents is the true stimulus, the procedure used to establish Equation 4 would have betrayed the fact by emerging with a co-efficient of zero for the inactive agent. Since neither of the co-efficients is zero, it must be concluded that both agents independently affect respiration."

The theory and the information given by this mathematical approach has proved itself useful, among other things, in estimating with accuracy the oxygen requirement at various altitudes, or equivalent altitudes, breathing varying percentages of oxygen, determining the efficiency of adding carbon dioxide to various gas mixtures, at differing altitudes. The information derived helps us understand, if only partially, the great many problems to be solved in pulmonary ventilation.

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# News Items

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## THE THIRD ANNUAL MEETING

The third annual meeting of the American College of Allergists was held June 6, 7 and 8 at the Hotel Senator, Atlantic City, just preceding the centennial session of the American Medical Association. The attendance exceeded that of all previous meetings. The attendance and enthusiasm aroused must be credited to Dr. Harold A. Abramson and his Program Committee, as well as to Dr. Charles Hyma, chairman of the Committee on Local Arrangements and his assistants. Although arrangements were made comparatively late, a very satisfactory number of manufacturers and distributors of products of interest to the allergists had advertisements in the printed program, as well as informal exhibits on the mezzanine floor during the session. Both of these new features helped to contribute to the success of the meeting.

The guest of honor, Dr. Gregory Schwartzman, Head of the Department of Bacteriology, Mt. Sinai Hospital, and Clinical Professor of Bacteriology, Columbia University, New York City, spoke at the Saturday afternoon session on "Phenomenon of Local Tissue Reactivity in Reference to Problems of Hypertensiveness and Evolution of Infectious Processes." The program was featured by the presentation of a round table and panel discussion on "Psychodynamics and the Allergic Patient" Sunday afternoon, June 8. Dr. Harold Abramson, Assistant Professor of Physiology, Columbia University, and Associate Professor of Allergy, Mt. Sinai Hospital, New York City, led the panel by reading a paper on the subject. The psychiatrists were represented on the panel discussion by the following: Dr. Frank Fremont-Smith, Medical Director, the Josiah Macy, Jr., Foundation, New York, New York, leader; Dr. Franz Alexander, Professor of Psychiatry, University of Illinois and Director, Chicago Institute for Psychoanalysis, Chicago, Illinois; Dr. O. Spurgeon English, Professor of Psychiatry, Temple University Medical School, Philadelphia, Pennsylvania; Dr. Sandor Rado, Clinical Professor of Psychiatry, College of Physicians and Surgeons, New York, New York; Dr. Edward Weiss, Professor of Internal Medicine, Temple University Medical School, Philadelphia, Pennsylvania; and Dr. J. A. P. Millet, Associate in Medicine, Columbia University, New York, New York. Representing the clinical allergists were: Dr. Rudolf L. Baer, Associate Attending Physician in Charge of Allergy Department, New York Skin and Cancer Unit, New York Postgraduate Hospital and Instructor in Dermatology and Syphilology, New York Postgraduate Medical School and Hospital, New York, New York; Dr. Ethan Allan Brown, M.R.C.S., London, L.R.C.P., England, Tufts College Medical School, Boston, Massachusetts; Dr. Hal M. Davison, Chief of Medical Division, Georgia Baptist Hospital, Atlanta, Georgia; Dr. Homer E. Prince, Associate Professor of Medicine, Baylor University School of Medicine, Houston, Texas; and Dr. M. Murray Peshkin, Instructor, College of Physicians and Surgeons, Post-Graduate Medical Extension, Columbia University, New York, New York.

As many members of the College as possible remained for the special session on allergy conducted by the AMA on Friday, June 13. There were about 450 present at this meeting. Dr. Harry L. Huber, Chicago, was chairman and Dr. Richard Kern, Philadelphia, secretary. The program was well balanced and highlighted by a panel discussion on "The Treatment of Asthma." Based upon the attendance and enthusiasm of this meeting one could reasonably expect that the Committee on Scientific Assembly of the AMA will seriously consider establishing a section on allergy and immunology in accordance with the request of the Academy and the American College of Allergists who appeared before the Reference Committee and the Committee on Section and Section Work. (J.A.M.A., July 20, 1946, Page 1000).

## NEWS ITEMS

The American Society for the Certification of Allergists met at the Hotel Senator, Friday evening, June 6, at which time announcement was made of the names of those men certified in allergy who form the founders' group. Up to the present time 116 allergists have been certified.

At the business session of the Board of Regents, it was decided that the fourth annual convention in 1948 would be held at the Hotel Pennsylvania, New York City, March 12, 13 and 14. Dr. M. Murray Peshkin is chairman of the Committee on Local Arrangements for this meeting, and Dr. Harold Abramson, chairman of the Program Committee. Since the annual meeting is to be held more than two months earlier than usual, it is urged that all members make their reservations as soon as possible by writing to the Secretary. Due to the fact that this meeting will be held so early in the spring, it was decided that a Spring Instructional Course would not be held and that all efforts would be concentrated upon the Fall Instructional Course to be held under the auspices of the University of Cincinnati, November 3-8, inclusive. A special reduction of 25 per cent will be given to all members of the College for Instructional Courses.

The Advisory Committee, which met at the Hotel Gibson, Cincinnati, March 30, made a report to the members of the Board of Regents. A list of the speakers available through the Speakers Bureau, which was initiated by the College some time ago, will be sent to the secretaries of the various state societies designating the qualifications of members to lecture and speak on allergy.

At the business meeting of the Board two members were elevated to active fellowship. The College now has almost 700 members, and the standards for elevation to full fellowship have been raised.

Some of the newer antihistaminic substances were reported for the first time at this meeting.

During the past year the College has been unfortunate in the loss, through death, of the following: Dr. Harry Greditzer, St. Louis, Missouri; Dr. Andrew M. Smith, Egg Harbor City, New Jersey; and Dr. Erich Urbach, Philadelphia, Pennsylvania. Obituaries have appeared in the *ANNALS* and condolences have been sent to the families.

The by-laws, as read and approved by the Board of Regents and recommended for adoption by the members of the College at the San Francisco meeting last year, were adopted and accepted in their present form.

The Nominating Committee, composed of three members of the Board of Regents and three members of the College-at-large, nominated one candidate for each elective office three months before the ensuing election. A ballot election was held in open meeting with instructions that additional nominations could be made from the floor. The following officers were elected to serve for one-year terms, July 1, 1947, to July 1, 1948: President, Dr. Hal M. Davison, Atlanta, Georgia; President-Elect, Dr. George E. Rockwell, Milford, Ohio; First Vice President, Dr. J. Warlick Thomas, Richmond, Virginia; Second Vice President, Dr. Robert F. Hughes, Hamilton, Ontario, Canada. The members nominated and elected to serve for three-year terms, July 1, 1947 to July 1, 1950, on the Board of Regents were: Dr. Harold A. Abramson, New York, New York; Dr. Jonathan Forman, Columbus, Ohio; Dr. John H. Mitchell, Columbus, Ohio; and Dr. Albert V. Stoesser, Minneapolis, Minnesota.

Dr. Leon Unger, President, called attention to the services which have been rendered to the College by the retiring members of the Board since its inception. By virtue of his position as Secretary-Treasurer, the Board appointed Dr. Fred W. Wittich an ex-officio member of the Board of Regents.

The business session adjourned with the introduction of the new President, Dr. Hal M. Davison.

**COMMITTEE FOR TESTING NEW AND UNUSED THERAPEUTICS**

At the meeting of the Board of Regents at Atlantic City, June 6, the Committee for the Testing of New and Unused Therapeutics, Dr. Ethan Allan Brown, chairman, was reorganized. It is planned to notify all pharmaceutical concerns that the Committee is ready to consider the investigation of drugs applicable to the treatment of allergic conditions. Pilot tests are to be done on small groups of private and clinic patients by several physicians working independently, and thereafter by selected workers in geographically distributed centers. Physicians interested in group investigations of this type are invited to communicate with the chairman of the Committee, listing their qualifications and the facilities at their disposal. The results of such investigations will give due credit to all of the contributing members.

**HONORARY FELLOWSHIPS**

Dr. Marie B. Morrow, of the University of Texas, Department of Botany and Bacteriology, has been elected an Honorary Fellow of the American College of Allergists by reason of her meritorious contributions to research in allergy in relation to atmospheric molds.

Dr. Morrow is engaged full time in teaching and devotes most of her time to Mycology. Over a period of approximately fifteen years, she has been very actively interested in mold allergy and has done invaluable work in this field. This interest has enabled the Association of Allergists for Mycological Investigations to conduct its studies in the field of mold allergy since the inception of the organization in 1938.

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Dr. Noble P. Sherwood, Professor of Bacteriology, School of Medicine, University of Kansas, has been elected an Honorary Fellow of the American College of Allergists, for his various contributions to research in allergy, immunology, and high attainments in the science of bacteriology.

One of the recent visitors to the headquarters of the College and of the International Association of Allergists was Dr. Zaida Eriksson-Lihr, Dr. Med. et Chir., Chief Physician of the Hospital for Allergic Diseases, Drumso, Finland. Dr. Eriksson is in charge of a new allergy hospital and clinic at Drumso.

The hospital was erected through private subscription. The library is greatly in need of literature, journals, and textbooks, on allergy, physiology, immunochemistry, et cetera. Any publications sent to the above address will be greatly appreciated.

At the regular meeting of the Chicago Society of Allergy, held on April 21, an election of officers was held and the following men were elected: Dr. Theodore B. Bernstein, President; Dr. Edward G. Tatge, President-Elect; Dr. Morris A. Kaplan, Secretary-Treasurer.

Any allergist wishing to secure a well-trained technician in the field of allergy, please contact the Secretary-Treasurer of the American College of Allergists, 423 LaSalle Medical Building, Minneapolis, Minnesota.

The Central Pennsylvania Allergy Association will hold its next annual meeting at Harrisburg, Pennsylvania, October 30, 1947. Dr. Stephen D. Locky, Lancaster, Pennsylvania, is president, and Dr. Ralph Mulligan, Reading, Pennsylvania, is secretary.

\* *In Memoriam* \*

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**HARRY GUS GREDITZER, M.D., F.A.C.A.**

We regret to announce the death of Dr. Harry Greditzer, September 27, 1946, at St. Louis, Missouri. He was born in Nevada, Missouri, December 4, 1889. After graduating from the Central High School in St. Louis in 1908 he attended Washington University School of Medicine from which he graduated in 1912. Dr. Greditzer interned at Washington University, was visiting surgeon at the St. Louis City Hospital, and assistant surgeon at the Maternity Hospital. He took post-graduate studies at St. Louis University in the Ear, Nose and Throat Clinic and later specialized as a Nose and Throat Allergist. He was an instructor in Urology at Washington University from 1914 to 1930. During World War I he was an instructor in Urology in the officers school there. He also held staff positions at the Children's Hospital, Jewish Hospital and St. Luke's Hospital, all of St. Louis.

Dr. Greditzer was a member of Phi Beta Pi, medical fraternity, and Alpha Omega Alpha. He was a member of the St. Luke's Medical Society, the Missouri State Medical Association, the American Medical Association, the American Urological Association, and the Southern Medical Association. He was a member of the medical staff of Washington University and assistant in surgery and surgeon to out-patients in the Genito-Urinary Department. He was elected a Fellow of the American College of Allergists in 1945.

Dr. Greditzer is survived by his wife, three sons, Harry G. Greditzer, Jr., David A., and Arthur S., and a grandson, Harry G. Greditzer, III.

The American College of Allergists is indeed sorry to lose this member of high standing, whose interest in the activities of the College has always been much appreciated.

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ALLERTEEN By W. L. Mermis, M.D. The Tenth Series of Letters of the International Correspondence Club of Allergy, X—page 109.

This is the report of an eight-months-old baby with an eczema of the lower extremities. The baby had a similar dermatitis at the age of about three weeks which was treated by a pediatrician who placed her on a soybean formula. The baby, however, was unable to tolerate this milk because of frequent watery bowel movements.

The baby was then placed on a goat's milk formula which corrected the character of the stools and there were normal bowel movements. However, the eczema did not improve but became worse, involving at this time both arms.

The baby was immediately placed on Allerteen, a soybean milk preparation which did not cause loose stools, and there was marked improvement in the eczema. After two months on this preparation, the dermatitis disappeared and at no time did the baby object to taking this form of milk.



## HORSE IMMUNOLOGY FOR ALLERGISTS

(Continued from Page 380)

globulin was obtainable on intravenous immunization; but the same antigen evoked non-precipitating antibodies upon subcutaneous treatment. It is pertinent that related observations were made in rabbits. They respond to the intradermal and subcutaneous introduction of pneumococci or streptococci with antibody versus the species-specific nucleoproteins rather than to the type-specific carbohydrates, whereas upon intravenous injections the inverse is true. The allergist would like to know more about the mechanisms involved in these findings, because he has so many difficulties in distinguishing between the modifying influence of the site of sensitization, and that of individual—that is genetically dominated—factors upon the type and manifestations of allergic disease.

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### ATOPIC CATARACT

(Continued from Page 363)

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# ANNALS of ALLERGY

*Published by the  
American College of Allergists*

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Volume 5

September-October, 1947

Number 5

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## NETHAPHYL IN THE TREATMENT OF NASAL ALLERGY AND BRONCHIAL ASTHMA

FRENCH K. HANSEL, M.D., F.A.C.A.

St. Louis, Missouri

IN the management of nasal allergy, allergic bronchitis and bronchial asthma, certain drugs must be prescribed to give the patient symptomatic relief. This is particularly necessary during the period of observation and study of the allergic problem involved. Sometimes it is necessary, especially in difficult cases, to continue to use drugs for an indefinite period of time. It is particularly desirable to use those preparations which are most effective, have the least side effects and to which there is little or no tendency to increased tolerance. The following clinical observations represent a supplemental report to that presented four years ago on the use of Nethaphyl.<sup>14</sup> During a period of seven years 47,000 tablets of this preparation and 24,400 tablets and capsules of the same with the addition of phenobarbital were dispensed to 750 patients, 150 of whom were children.

In the previous report, the pharmacology of the above preparations was presented in detail. It should be sufficient, therefore, to review only briefly the essential characteristics of these preparations.

### NETHAMINE HYDROCHLORIDE

This preparation is chemically methylethylamino-phenylpropanol and has essentially the pharmacological action of ephedrine. The degree of action in the bronchioles and the respiratory stimulation is the same, whereas it produces no noticeable pressor action and only a minimum degree of central stimulation.<sup>1</sup> Craddock<sup>4</sup> has shown that nethamine, in a series of eleven allergic patients sensitive to ephedrine and adrenalin or both, produced efficacious results and was tolerated without any undesirable side actions in all but one patient. Friedman and Cohen,<sup>5</sup> com-

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<sup>14</sup>"Nethaphyl" is a registered trademark of The Wm. S. Merrell Company for a combination of Nethamine (methylethylamino-phenylpropanol) Hydrochloride and Butaphyllamine (theophylline aminoisobutanol).

pared nethamine with ephedrine in forty-six allergic patients and found that the toxic effects were much more numerous with ephedrine, particularly in regard to central nervous stimulation. Clinically, nethamine seemed to be as efficacious as ephedrine but with much fewer side actions.

#### BUTAPHYLLAMINE

This preparation is chemically theophylline aminoisobutanol and offers certain improvements in stability and solubility in comparison to other compounds of similar nature. It contains approximately 67 per cent theophylline and the toxicity in the experimental animal is approximately of the same order as that of aminophyllin.<sup>13</sup> Steinberg and Jensen,<sup>11</sup> in studying the use of this compound in angina pectoris, found it to be somewhat better tolerated than other theophylline compounds. Smith and Jensen<sup>10</sup> demonstrated its value in experimental heart failure in producing striking stimulation of the myocardial contractions and in causing rapid removal of the pulmonary edema and congestion resulting from heart failure experimentally induced. Steinberg and Jensen,<sup>12</sup> in a later report, demonstrated that theophylline aminoisobutanol caused a fall in venous pressure and a shortening of circulation time. These effects were more pronounced when these functions were elevated above normal.

These studies seem to indicate that butaphyllamine has the basic action of other theophylline derivatives with the possible advantages of better toleration.

#### THEOPHYLLINE DERIVATIVES IN ASTHMA

The pharmacologic basis for the use of theophylline preparations in the treatment of bronchial asthma was demonstrated by Young and Gilbert.<sup>14</sup> In a clinical study of sixteen patients, Herrmann and Aynesworth<sup>7</sup> employed the intravenous route of administration. They made the observation that in one patient in whom the injection failed to give relief, adrenaline was of benefit as a subsequent injection although the patient had been previously refractory to it. Hyman<sup>8</sup> also made this observation. Theophylline apparently overcomes the refractoriness to adrenalin. Carr<sup>3</sup> and also Brown and Blanton<sup>2</sup> reported the effectiveness of theophylline preparations in adrenalin-fast patients.

In a critical study on the use of theophylline mono-ethanolamine in the treatment of bronchial asthma and other allergies, Lamson and Bacon<sup>9</sup> presented their observations on a group of 153 patients. They recommend the administration of the smallest effective dose, to be repeated only when necessary. Small doses minimize unpleasant side effects. Adrenalin-fast patients responded satisfactorily, and after one year it was not necessary to increase the dosage to obtain the same degree of relief. In a group of 112 patients, 77 per cent had definite and complete relief of symptoms on a total dose of 0.26 Gm. or 4 grains in twenty-four hours. Untoward side effects were inconspicuous. Gnaw-

ing sensation in the epigastrium, nausea and sometimes vomiting were the chief untoward effects, but these did not occur when the medication was taken with food. Occasionally tachycardia occurred.

#### CLINICAL OBSERVATIONS

The following observations are based upon a study of 750 cases of allergic bronchitis and bronchial asthma in which nethamine and butaphyllamine were employed as an adjunct in allergic management. One hundred fifty of the 750 patients were children varying in age from two to fourteen years. These studies were conducted over a period of seven years, during which time the following were administered: Nethamine  $\frac{3}{4}$  gr. and butaphylline 2 gr., 38,400 tablets; nethamine  $\frac{3}{4}$  gr. and butaphylline 1 gr., 8,600 tablets; nethamine  $\frac{3}{8}$  gr., butaphylline 1 gr. and phenobarbital  $\frac{1}{4}$  gr., 18,400 capsules and nethamine  $\frac{3}{4}$  gr., butaphylline 2 gr. with phenobarbital  $\frac{1}{4}$  gr., 6,000 tablets. Inasmuch as the majority of patients, especially the children, had nasal as well as bronchial symptoms, the combination of the two drugs was found to be more satisfactory than using the latter alone.

In a significant number of patients with chronic cough, without definite nasal symptoms or bronchial asthma, the cause may be explained on an allergic basis. In children there is not infrequently a history of chronic cough before the onset of definite asthma. None of these patients is satisfactorily relieved by the usual cough mixtures containing narcotics.

We have found that these patients usually responded to the administration of nethamine and butaphyllamine suggesting an allergic cause which could be proved by an allergic investigation.

The results obtained in this series of cases confirm those reported by others on the use of theophylline compounds in the treatment of bronchial asthma. On the whole, our studies were conducted on a basis similar to that reported by Lamson and Bacon<sup>9</sup> in that an attempt was made to establish the minimum effective dosage. At the same time, patients were instructed to take the medication only when necessary. When continuous administration was indicated, the doses were recommended every three to four hours. In general, the average optimum dosage in adults was nethamine  $\frac{3}{4}$  gr. and butaphyllamine 1 gr. Some patients required twice this dosage, rarely larger. Those patients who complained of insomnia or palpitation were given the tablets or capsules containing in addition  $\frac{1}{4}$  gr. of phenobarbital. The average dosage in children from four to twelve years of age was nethamine  $\frac{3}{8}$  gr. and butaphyllamine  $\frac{1}{2}$  gr. Occasionally it was necessary to double this amount. The length of time the medication was continued varied considerably in the entire group. Those patients who responded promptly to allergic methods of management were able to discontinue the medication within a short period of time. In the more difficult cases, in which response to man-

agement was slow or in the case of those patients who never became entirely free of bronchial asthma, the medication was continued for several years, the longest about seven years. In these instances, there was no tendency noted to increase tolerance to the medication.

The untoward side effects from this compound were clinically insignificant (or inconsiderable); epigastric distress, nausea or vomiting occurred only occasionally, but these reactions could usually be eliminated when the medication was taken with food or the dosage decreased. Unlike ephedrine combinations, this product rarely produced palpitation and only occasionally did the patient experience insomnia. The very infrequently occurring nervousness and insomnia could easily be controlled by the administration of the tablets or capsules with phenobarbital added. A number of patients could take nethaphyl who could not tolerate ephedrine combinations. So far no case of sensitivity to nethaphyl has been observed.

In the treatment of bronchial asthma, nethaphyl is far superior to benadryl, pyribenzamine and similar preparations. Although the latter compounds have been very effective in the relief of hay-fever symptoms, the observation has been made by a number of allergists that complicating asthma more frequently occurs from over-use of these drugs. Prolonged vasoconstriction of the nasal mucosa apparently decreases the filtering function of the nose as a result of which more pollen enters the bronchial tree.

#### SUMMARY

1. A study of the use of nethaphyl (nethamine hydrochloride, and ephedrine-like compound, and butaphyllamine, a theophylline derivative) in the treatment of nasal allergy and asthma in 750 patients extending over a period of seven years is reported.
2. The effectiveness in the relief of symptoms has been most satisfactory.
3. Untoward side effects were inconspicuous.
4. Minimum or optimum doses are recommended.
5. Repeated administration has not necessitated an increase in dosage.
6. On account of the high solubility of these drugs, absorption is rapid and responsiveness is prompt.

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## ASKS AID IN NURSING CRISIS

Katharine J. Densford, president of the American Nurses' Association, has urged the governors of all forty-eight states to call state-wide conferences "at the earliest possible date" to consider concrete measures to resolve the nursing crisis created by increased demands for nursing service now facing the American public.

Pointing out that the nursing profession is united on a program of action, Miss Densford, in telegrams to each governor, called for effective action in every state of the union. Her message follows:

"I made a nation-wide telephone roll call from Minneapolis on October 20 to get the support and co-operation of the forty-eight presidents of the state nurses' associations. The ANA, representing 155,000 professional registered nurses, received wholehearted support from the state association presidents on three major points of the ANA's program: (1) Make nursing care equally available to all by intensifying efforts of the ANA's counseling and placement service for the best possible use of available nursing service, and provide a continuing supply of nurses by promoting recruitment; (2) improve nurses working conditions, rates of pay, personnel practices, and see that nurses share in the administration of nursing services; (3) protect the public by adequate legal control of nursing practice, both professional and practical.

"We in ANA are doing everything in our power to rouse the public to a clearer understanding of the nursing crisis, because nurses cannot singlehandedly solve the problem. Effective action is needed at once in every state of the union. As president of the American Nurses' Association I am respectfully requesting the governors of each state to co-operate with us.

"Specifically, I ask you to call on the president of your state nurses' association, and the head of every group interested in public health and public service, to meet at a state-wide conference under your auspices at the earliest possible date to consider concrete measures resolving the nursing crisis now facing the American public. I shall deeply appreciate a prompt reply from you indicating what co-operation you can give this public situation."

## THE SKIN-TEST BLOCKING ANTIBODY RESPONSE TO ORAL POLLEN THERAPY AND THE CRITERIA FOR ITS USE

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With the Technical Assistance of

MISS HELEN A. FLAHERTY

SINCE its initiation by Noon in 1911, no other form of treatment has seriously challenged the position of injection therapy for the treatment of pollen sensitivity. The presence of immunological changes following the injection of pollen extract has been demonstrated by Harley<sup>11</sup> and measured by a number of workers; chiefly by Loveless<sup>17-21</sup> and by Cooke and Sherman.<sup>7</sup> Exact correlation between antibody titer and clinical improvement has, however, been questioned by Black<sup>4</sup> and others, and it is the present opinion that such relationships are highly individual. Although there is no doubt that the heat-stable blocking antibody appears as a result of injections of pollen extract, there is no certainty that either its presence or its quantity is a measure of immunity, especially since injection treatment is known to cause simultaneous increase in the reagin content of the blood of some subjects. The degree of hyposensitization may therefore lie in the proportional increase of what appears to be a double type of response to a single botanical, but actually an immunologically multiple biochemical stimulus.

Unsatisfactory as the present state of our knowledge may be for injection therapy, that of oral pollen treatment is, if anything, less satisfying, since the results reported are almost entirely clinical.

Gatterdam,<sup>10</sup> using a phosphate glycerin pollen solution, given orally, reported that his patients achieved 90 to 100 per cent relief. Hartmann<sup>12</sup> tabulated excellent results following the use of tablets composed of the seeds and flowers of plants causing hay fever. Rockwell,<sup>22,23</sup> who stated that oral pollen dosage should be 50 to 100 times greater than that given by injections, was able to demonstrate satisfactory results in 115 patients, with fair results in twenty-three, and no relief in forty-four. Greater improvement was described by Schwartz,<sup>24</sup> of whose sixty-five patients, 40 per cent were completely relieved, and 47 per cent satisfactorily relieved, while only 13 per cent had poor results. Conway,<sup>9</sup> with 1,600 patients, reported 94 per cent as completely free of symptoms.

The negative reports are equally impressive. Bernstein and Feinberg<sup>3</sup> observed that the gratifying results were achieved in areas of low pollen concentration. Of their twenty patients treated co-seasonally with oral pollen, eighteen were complete failures. The asthmatic patients did not respond in any measurable degree. Of forty patients studied by Black<sup>4</sup>

The expenses incurred by this study were defrayed, in part, by The Asthma Research Foundation, Inc., of Boston, Massachusetts.

only 40 per cent demonstrated satisfactory improvement. Three of these who were unable, at first, to take hypodermic injections, after pollen ingestion tolerated injection therapy. Alperstein<sup>2</sup> was able to show that oral therapy was more effective in those who had previously been given injections as compared with those who had no previous treatment. His comparisons, however, show injection treatment as much more satisfactory, although oral treatment gave, in some patients, considerable relief. In a later co-operative study, Feinberg and his associates<sup>9</sup> demonstrated that occasional patients, given placebos, reported results comparable to those taking pollen orally. Iliff and Gay<sup>14</sup> and Bohner<sup>5</sup> concurred that injection therapy was the more satisfactory form of treatment.

Although Eyerman<sup>8</sup> has suggested that any type of therapy must be applied to the same patient for at least five years before its value can be estimated, an analysis of these reports, limited at the most to one season, demonstrates that although the consensus favors injection treatment, the results with both forms of therapy illustrate the well-known clinical fact that patients do both poorly or well on both high or low doses of both the injection or oral types of treatment. It occurred to us that it might be possible to advance our clinical knowledge if immunological procedures could be used to demonstrate other than clinical responses to oral pollen therapy.

It has been shown by Loveless (*op. cit.*) that the blocking antibody appeared as a result of injection treatment. Alexander and his associates,<sup>1</sup> confirming its presence, stated that generally the relief from hay fever seemed to be due to a high thermostable antibody titer. In their subjects, the reagin titer was not correlated to the thermostable antibody of circulatory antigens. On the other hand, Scully and Rackemann<sup>25</sup> had concluded earlier that no correlation could be found between the amount of blocking antibody produced as a result of treatment and the clinical relief of symptoms, and that the therapeutic effects of ragweed extract therapy are not due to the production of such antibody. An examination of the techniques followed suggests that they differ from those first described by Loveless.<sup>18</sup>

There are also differences of opinion concerning the effects resulting from the ingestion of pollen. London<sup>16</sup> failed to find any evidence of the presence of ragweed pollen protein in the blood stream following its oral administration. Zeller<sup>27</sup> concluded that the only available evidence of enteral absorption of pollen is the constitutional reactions which are encountered following its ingestion. Thiberge,<sup>26</sup> who tested sensitive subjects intracutaneously with both ordinary pollen extracts and extracts artificially predigested with gastric, intestinal and pancreatic enzymes, concluded that gastric digestion destroys some of the antigenic power of ragweed pollen. Hecht<sup>13</sup> and his co-workers, studied the reactions produced in passively sensitized skin sites, their results indicating that a relationship existed between the gastric acidity and the pollen absorption. Sixteen patients



with low acid values absorbed sufficient pollen to produce reactions in passively sensitized sites, while six with normal acid values did not absorb sufficient antigen to produce reactions. Of interest in this report is the work of Levin and Shulsky,<sup>15</sup> who showed that eleven of thirteen children, injected hypodermically with ragweed pollen, demonstrated an increase in the neutralizing capacity of the serum and nine showed an increase in the skin sensitizing ability of the serum. In ten children treated orally (240,000 Noon units daily), nine showed an increase in the neutralizing capacity of the serum and all ten showed an increase in the skin sensitizing ability of the serum. The results therefore indicated that pollen taken orally in adequate quantities is absorbed from the gastrointestinal tract and that the succeeding changes are similar to those occurring in patients treated hypodermically.

The conclusions drawn from the literature indicated that further work in this field appeared to be warranted.

In all, twenty patients were chosen for study. Of these, six ceased treatment, leaving fourteen who could be used for investigative purposes. Of these, nine were male, of whom five had hay fever and the remainder both hay fever and bronchial asthma. Of the six females, only one suffered from an uncomplicated hay fever, and five both from hay fever and bronchial asthma. The ages ranged from nine to twenty-five, with one patient aged forty-two and one aged sixty. All had had symptoms for more than one season, but none had had either skin tests or injection treatment. For all of the subjects studied, the history was taken by one worker, the treatment given by a second, and the serum titrated by a third. The skin and conjunctival tests were done by a skilled technician, who also took blood for titration purposes before skin-testing the patient for the first time, and subsequently during the treatment period, as well as following the cessation of treatment. The patients reported on their progress and also kept symptom diaries. In order to discover whether the oral pollen therapy would affect the skin tests, all of the patients were tested on the occasion of their first visit, and on three or more subsequent visits. The tests were done intracutaneously and with fresh extract standardized in PNU. So that minor changes could be measured, the successive gradations were made smaller than usual, the strength in units measuring 0.05, 0.1, 0.5, 1, 5, 10, 50, 100, 150, 200, 350, 500, 750, 1,000, 1,500, 2,000, 3,500, and 5,000 units. A wheal with pseudopodia and a flare was defined as a positive reaction and in each case a test was done with higher concentrations, in order to corroborate the positive reactions. Conjunctival tests were done with increased concentrations; 100, 150, 200, 350, 500, 750, 1,000, 1,500, 2,000, 3,500 and 5,000 PNU of freshly prepared ragweed pollen extract, the less injected eye being chosen.

Blood was taken on the first visit and before the patient was tested, and on subsequent days during the treatment period and during the ragweed

pollen season and in seven patients two to three months post-seasonally. The blood was taken at least three days following pollen ingestion. The serums were labeled A and P<sub>1</sub>, P<sub>2</sub>, and P<sub>3</sub>. The technique followed for antibody titration is essentially that described by Loveless<sup>18</sup> and by our previous communication to this journal (*Ann. Allergy*, 2:207, 1944).

The rationale of the technique is based upon the fact that the quantity of the immune antibody present in the serum of a treated allergic patient can be measured by two methods. The first is an estimation of the capacity of the serum to inhibit the reaction which would naturally occur when a passively sensitized subject is tested with free antigen. If the antigen is completely bound, no reaction will occur, but in such sites in which reactions do occur, the degree of response will be proportional to the amount of immune antibody present. Secondly, the same sites can be reinjected with an excessive amount of antigen. In those sites, in which the first antigen injection was bound and completely inactivated, the reagin is still present in its original amounts and the injection of excessive antigen will produce a maximum reaction. In those sites in which the antigen first injected was not completely inactivated so that some combination of reagin and antigen occur, there would be a lesser amount of reagin present. The injection of an excessive amount of antigen would result in a noticeably smaller reaction. For quantitative studies, all sites are sensitized with equal amounts of the same ante-treatment serum. To maintain the reagin content of all the sites equal when post-treatment serum is added, the contained reagins are destroyed by heating at 60° C. for one hour.

The tablets used were prepared for us by Brewer and Company (Worcester, Mass.) and were made to contain sufficient pollen to be equivalent to 1,000, 10,000, and 30,000 PNU with an enteric coating designed to disintegrate in the alkali of the small intestine three to five hours following ingestion. They were colored red, white, and blue, so that the respective strengths could not be mistaken. Each patient received initially twenty-four red tablets, with instructions to take one, two, three, four, six, and eight tablets after the largest daily meal at three-day intervals, the days being termed as one, four, seven, ten, thirteen and sixteen. The successive doses were therefore 1,000, 2,000, 3,000, 4,000, 6,000 and 8,000 PNU. On his return, if no symptoms referable to the gastro-intestinal or respiratory tracts had occurred, the patient received twenty-four white tablets, one to be taken on that day (the nineteenth) and then every third day to the forty-third day; two tablets (20,000 PNU) on the twenty-second day; and thereafter three tablets (30,000 PNU) for each successive dose every three days. On the patient's third visit, twenty-four blue tablets, each representing 30,000 PNU, were dispensed, one tablet to be taken that day, two tablets three days later, and three tablets (90,000 PNU) every third day thereafter. By the seventy-second day, the patient had taken seventy-two tablets representing a minimum dose of approximately

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TABLE I. DOSAGE SCHEDULE (PRESEASONAL)

Day	Dose	Total PNU Units	Color	No. Tablets
1	1	1,000	Red	1
4	2	2,000		2
7	3	3,000		3
10	4	4,000		4
13	5	5,000		5
16	6	6,000		6
19	7	10,000	White	1
22	8	20,000		2
25	9	30,000		3
28	10	30,000		3
31	11	30,000		3
34	12	30,000		3
37	13	30,000		3
40	14	30,000		3
43	15	30,000		3
46	16	30,000	Blue	1
49	17	60,000		2
52	18	90,000		3
55	19	90,000		3
58	20	90,000		3
61	21	90,000		3
64	22	90,000		3
67	23	90,000		3
70	24	90,000		3
72 days	—24—	984,000 PNU		72 Tablets

1,000,000 PNU. Some patients continued the blue tablets, taking three at mealtime for some weeks or months longer, reaching a maximum of 6,000,000 to 7,000,000 PNU. The dosage schedule is tabulated in Table I.

The exact technique for the immunological studies can be outlined as follows:

1. The "A" (ante-treatment) serum was collected before the patient's first skin tests for ragweed pollen sensitivity were done. The serum was then stored in the ice box. Hinton reactions and bacterial cultures insured sterility. No experiments were performed during the pollen season.

2. The "P" (post-treatment) serum specimens were collected according to the dates on the accompanying table, the first date being that of the skin tests, and the other dates at widely separated intervals, including one, whenever possible, during the pollen season, and another several months later.

3. The "P" serum was heated for one hour at 60° C. in a constant temperature bath, in order that all demonstrable skin sensitizing reagents might be destroyed.

4. The vials were set up in series; with chemically clean sterile 0.25 ml. pipettes. One series of vials was instilled with mixtures of constant amounts of autogenous serum "A" and progressive dilutions of the ragweed extract; another series with mixtures of constant amounts of autogenous serum "A," heated serum "P," and the progressive dilutions of ragweed extract. Saline was added to the first series to keep the volume relationships constant in all testing mixtures. The "A" serum added to the heated serum in the second series is, in almost every instance, the patient's own "A" serum. Two volumes of buffered saline were added to the serum used in the control mixture. After the ingredients were mixed, the vials were permitted to stand for one hour.

5. Using the skin on the back of the test subject, known by history and skin tests to be nonatopic, 0.1 ml. from each vial was injected for a series of ten sites. These sites are 3 inches apart and do not come within 2 inches of the spine. A graduated 1 ml. tuberculin syringe is considered sufficiently accurate for performing the injections. The test subjects are not used more than once.

6. The reactions are read at fifteen to thirty minutes, within which period the serum control sites are practically negative. In some instances, however, the non-specific irritation did not subside before the specific reactions reached their maximum.

7. After twelve to eighteen hours, when practically all signs of the first test had disappeared, each test site was reinjected with 0.025 ml. of the dilution of ragweed extract containing 10,000 PNU/ml. For these injections, a 0.25 ml. tuberculin syringe was used, the needle point being inserted into the same puncture orifice produced by the previous sensitizing injection.

8. The reactions were observed at ten-, twenty-, thirty- and forty-minute intervals. When the nonspecific reactions appeared minimal and the specific reactions maximal, the sites were graded as 1, 2, 3, or 4 plus. The sites were then traced and photographed. The titer of the given unheated serum, or a mixture of this serum with a heated serum, is expressed in a number of units of antigen originally present in the site, which, on subsequent testing, gave a plus-minus reaction. The last positive reaction, or plus-minus reaction, is taken for the end point. This was done to make certain that an end point was not taken too far beyond the first negative response attainable. The technique given above is similar to that given in our earlier paper on this subject (*loc. cit.*).

Analysis of the clinical results, taken from the patient's own impressions, shows seven who claimed no or slight improvement, and of an eighth who could not be certain of change and who is, therefore, classified with this group. In this same group, one patient stated that it was the worst year he had ever suffered. Six other patients concluded that they had had slight symptoms, some commenting that the treatment had given them excellent results.

It was thought that the data could be studied more effectively if the patients were classified as either very much improved or very much worse rather than trust our judgment to what might be a moderate or fair response. Any symptoms termed more than slight were considered as a poor result. Irrespective of the clinical results, immune bodies were present in only one ante-treatment serum, which consistently required 10 units of ragweed pollen extract for neutralization in each of three tests. In all of the others, no antibodies were present before treatment. In all of the patients, however, without exception, oral pollen ingestion caused an increase in heat stable blocking antibody, requiring for its neutralization an amount of antigen equivalent to a solution varying from 25 to 1,000 PNU. It can therefore be concluded, although tentatively, that pollen ingestion does cause the development of a blocking substance which does not apparently differ from heat stable blocking antibody. The relationship of its presence and amount to the patient's clinical symptoms is, however, not clear.

The first two patients in the second table (C. H. and M. W.) presented final respective responses of 25 and 50. Each claimed poor results, the second stating that he had had the worst year he had ever experienced. The third patient (R. P.), for a titration point of 50, reported only slight symptoms and much improvement.

TABLE II.

Patient	Date of serum collection	PNU antigen required to neutralize 1 ml. "A" serum	PNU antigen required to neutralize 1 ml. "A" serum and 1 ml. heated "p" serum	PNU antigen required to neutralize 1 ml. "A" serum	PNU antigen required to neutralize 1 ml. "A" serum and 1 ml. heated "p" serum	PNU antigen required to neutralize 1 ml. "A" serum	PNU antigen required to neutralize 1 ml. "A" serum and 1 ml. heated "p" serum
L. H.	2.14.44	0	0	0	10-25	0	25
	4.24.44						
	6.26.44						
	8.7.44						
M. W.	12.27.43	0	0-10?	0	25-50	0	50
	3.10.44						
	3.27.44						
	8.7.44						
R. P.	12.13.43	0	0	0	50	0	50
	5.1.44						
	6.30.44						
	12.11.44						
G. S.	12.27.43	0	0	0	100-250	0	100
	3.11.44						
	7.17.44						
	11.6.44						
W. Ka.	12.3.43	0	25	0	100	0	100
	2.25.44						
	6.6.44						
	12.29.44						
M. B.	11.29.43	0	0-10	0	50	0	250
	2.7.44						
	6.19.44						
	8.11.44						

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W. Kc.	11.29.43 2.11.44 6.16.44 8.21.44	0	10-25	0	25	0	250
L. F.	12. 6.43 12.21.43 11.25.44 12.22.44	0	25-50	0	250	0	250
F. DeB.	11.29.43 2.14.44 3.19.44 8.18.44	0	10	0	50	0	100-250
M. H.	12.16.43 2.18.44 6.30.44 12.15.44	0	10-25	0	100	0	250
L. R.	12. 3.43 2.14.44 8. 7.44 12. 1.44	0	0-10	0	50	0	500
W. B.	12. 6.43 2.21.44 4.28.44 8.11.44	0	0-10?	0	50-100	0	500-1000
J. C.	12.13.43 12.28.44 5. 1.44 10.10.44	10	25	10	100-25	10	500
G. B.	12. 3.43 2.11.44 6.16.44 8.11.44	0	10-25	0	100-200	0	1000

The fourth and fifth patients (G. S. and W. K.), with end points of 100, reported excellent results, and the latter "the best year yet."

The next four patients (M. B., W. K., L. F., and F. DeB.), with titration points of 100 and 250, showed no improvement, while the tenth patient (L. H.) was much improved for the same immune response.

The eleventh and twelfth patients (W. B. and L. R.), for a response of 500 to 1,000, showed no improvement, while the thirteenth (J. C.), for 500, claimed his best year. The last patient (G. B.), for 1,000, had great improvement. It is apparent that for each level of response there are both equally poor and excellent results. The titration reactions of a typical patient (M. H.) are demonstrated in the third table.

Is there a relationship to the patient's initial syndrome? Four subjects suffering from pollen hay fever and bronchial asthma showed no improvement, and four presenting the same syndrome, were markedly better. Three with simple hay fever reported no improvement, while three were noticeably free of symptoms.

Two patients complained of gastric upsets, and one additional subject stated that nausea and vomiting followed the ingestion of the tablets when three of the white were taken. She also felt that her bronchial asthma was much more severe on the day of medication.

One patient (G. S.) attributed a bout of diarrhea to the tablets, but continued their ingestion without further symptoms and reported an excellent season.

It was hoped that long-term studies could be done, but early in 1947 we were successful in discovering the present status of only five patients, four of whom took subsequent injection treatment with good results, while the fifth, who had achieved relief following oral therapy, was still doing well without treatment.

In the fourteen patients for whom there was sufficient data, correlations between skin tests, eye tests, antibody titer, and clinical results were sought.

For L. H., the successive intracutaneous skin tests at intervals of two months gave reactions at levels of 10, 50, 50, and 100 PNU, while conjunctival tests were respectively 200, 200, and 350 for positive reactions and negative at 5,000 PNU on one occasion for eight months of pollen ingestion. For a treatment total of 3,000,000 units and a titer of 25, there was no improvement.

For M. W., who had successive skin tests from December 27, 1943, to August 7, 1944, and reacted consistently at the 30 PNU level for ophthalmic tests which reacted equally consistently at 50 to 100 PNU, there was a treatment total of 6,000,000 units and a titer of 50, with no improvement.

The third patient (R. P.) demonstrated a change in skin tests, reacting on December 3, 1943, to 200 PNU, on February 8, 1944, to 350 PNU, and on March 24, 1944, to 1,000 PNU. The tests were thereafter nega-

TABLE III. EXAMPLE OF TITRATION REACTIONS

Patient No. 10 (M.H.)

PNU	Initial		12-hr. Reinjection		Initial	12-hr. Reinjection	Initial	12-hr. Reinjection
	"A" Serum	"A" and Heated "P"	"A" Serum	"A" Serum Heated "PV"	"A" and Heated "P"	"A" and Heated "P"	"A" and Heated "P"	"A" and Heated "P"
10	3-4 plus	4 plus	exhausted	2 plus	2 plus	3 plus	1 plus	4 plus
25	3 plus	4 plus	0	1 plus	3 plus	3 plus	2 plus	3 plus
50	3 plus	4 plus	plus/minus	1 plus	2 plus	1-2 plus	3 plus	4 plus
100	4 plus	4 plus	plus/minus	1 plus	4 plus	plus/minus	3 plus	2 plus
250	3-4 plus	4 plus	1 plus	1 plus	4 plus	plus/minus	4 plus	plus/minus
500	4 plus	4 plus	1 plus	1 plus	4 plus	plus/minus	4 plus	plus 1
1000	4 plus	4 plus	1 plus	1 plus	4 plus	1-2 plus	4 plus	1 plus
1500	4 plus	4 plus	plus/minus	1 plus/minus	4 plus	1 plus/minus	4 plus	1 plus
Control	0	0	4 plus	4 plus	0	4 plus	0	4 plus

tive to solutions of 5,000 PNU. There was no ophthalmic test at any time and for a total dose of 4,000,000 and a titer of 50, he was much improved.

For the fourth patient (G. S.) the skin tests reacted at 0.5 PNU level and the ophthalmic test at 150 PNU. No further tests were done, but for a dose of 1,000,000 units and a titer of 100, he did exceedingly well.

The next patient in the series (W. Ka.) demonstrated progressive decreases in skin-test reactivity; his first initial test showing a response to 750 PNU on November 7, 1943, and a skin response only to 5,000 PNU on August 7, 1944. At no time was there a conjunctival test. For a total dose of 6,000,000 units and a titer of 100, he was much improved. (His "A" and "P" serums were graciously titrated for us by Dr. Mary Loveless, whose data showed a similar increase in titer, although her figures were higher than ours.)

On the other hand, M. B. demonstrated some change in skin reactivity; his test varying from an initial level of 100 PNU to a post-treatment reaction of 500 PNU. The conjunctival test was negative. For a total dose of 4,000,000 units and a titer of 250, there was no change in his symptoms.

Another patient (W. Ke.) demonstrated no change in skin tests, which remained at the 200 PNU level for ophthalmic tests which were constant at 500 PNU. For a total of 4,000,000 units and a titer of 250, there was no improvement.

For the next three patients, L. F. also presented no skin or ophthalmic test changes, the former remaining at 50 to 100 PNU and the latter at 350 to 500 PNU. With a total dose of almost 7,000,000 units and a titer of 250, he suffered severe symptoms. (For his serums, the titer as corroborated by Dr. Mary Loveless, was comparable to our own, although our end point was lower.)

For F. DeB., the skin tests and ophthalmic tests stayed at respectively 100 to 150 and 500 to 750 PNU. The total dose of 6,000,000 and a titer of 100 to 250 were associated with no improvement.

The tenth patient (M. H.) showed slight change in skin tests which



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TABLE IV. A CORRELATION BETWEEN SKIN TESTS, EYE TESTS, AND CLINICAL COURSE

Patient	Skin Test Decreased	Skin Test Same	Eye Test Decreased	Eye Test Same	No Eye Test	Improved	Worse
1	X		X				X
2		X		X			X
3	X				X	X	
4						X	
5	X				X	X	
6	X				X		X
7		X		X			X
8		X		X			X
9		X		X			X
10	X		X			X	
11		X		X			X
12	X			X			X
13	X				X	X	
14	X				X	X	

responded initially to 50 PNU and finally at 150, a probably insignificant variation. The ophthalmic test changed, however, from a reaction of 500 to one of 1,500. For a dose of 5,000,000 and a titer of 250, the patient claimed marked improvement.

The next patient (L. R.), with skin tests which remained stable at 50 to 100 and an ophthalmic test which varied in reactivity from 350 initially to 750 finally, for a titer of 500 and a dose of 6,000,000, showed no improvement.

The twelfth patient (W. B.) changed in skin-test reactivity from an initial 50 to a final 200 to 350 PNU level. The conjunctival test varied from 150 to 750 PNU, but for a dose of 6,000,000 and a titer of 500 to 1,000, there was no improvement.

The thirteenth patient (J. C.) apparently changed in skin-test reactivity, the successive levels of response being 150, 100, 1,000, 500, 1,000 PNU. There was no eye response. For a dose of 6,000,000 and a titer of 500, he claims his best year of symptom freedom.

The final patient of the series showed an unusual reversal, the successive skin test reactions being 100, 50, 1,000, 500, and 50. The ophthalmic test was negative. For a dose of 6,000,000 units and a titer of 1,000, he was much improved, both for his hay fever and bronchial asthma.

There are these variables to consider: Was the skin test increased or decreased? If an ophthalmic test was present, did it increase or decrease? Was there any relationship between these, the dose, the antibody titer, and the patient's progress?

An analysis of the data brings out the following suggestive conclusions: Two patients (M. H. and L. H.), whose skin test and ophthalmic test decreased were, one of them better for a titer of 200, and the other worse for a titer of 10. No valid conclusion can be drawn from two patients, but it might appear that the higher titer could perhaps represent a higher immunity.

Further studies show that in four patients in whom there was a decrease in the skin test and no ophthalmic tests were present, all improved,

although the titers were respectively 50, 100, 250, and 500. The absence of an ophthalmic test with a decrease in the skin-test reactivity is apparently associated with improvement, independently of the titer levels, although a fifth patient (G. B.), with a skin-test decrease, and then an apparent increase in sensitivity with no additional eye test and titer level of 1,000, was also among the improved.

In five patients, in whom the skin tests remained at the same level, the ophthalmic test was present and did not change, and in the sixth patient, in whom the skin tests decreased slightly, but with no change in ophthalmic reaction, there was no improvement. For this group, the titer levels were respectively 50, 100 to 250, 250, 250, 500 and 500 to 1,000. Since the titer levels are of the same order in both groups, no apparent relationship can be said to exist. In one patient serial dilution skin tests were not done, and his results are not with either group.

From this small group of fourteen patients suffering from hay fever and bronchial asthma, and studied intensively over a period of several years, the following tentative conclusions can be drawn regarding oral pollen therapy.

In all, an unexpected apparent blocking antibody response occurred. This level was not apparently related to the patient's clinical progress, since it was not consistently high in those who improved, or low in those who were worse.

In seven patients there was an unexpected decrease in skin test sensitivity, and in an eighth, an apparent reversal of the skin tests. In two subjects, there was a decrease in ophthalmic sensitivity.

In those patients in whom no ophthalmic test was present and the skin test sensitivity apparently decreased, there was marked improvement. In two patients in whom ophthalmic tests were present, and both they and the skin test decreased, one reported improvement and the other none. When the ophthalmic test was present and remained unchanged, no improvement occurred.

In the five patients in whom ophthalmic tests were present, and both they and the skin tests remained at the same level, no improvement, of course, was seen. In other words, with two exceptions, in the patients who gave no positive conjunctival tests, or in whom the skin and conjunctival tests decreased, there was improvement following oral pollen treatment. In those in whom conjunctival tests were present and remained unchanged, improvement did not occur.

A four-year follow-up of the remaining patients gave no significant long-range variations. One patient reported that he was still well, and others of the group took injection treatment with good effects.

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## ORAL POLLEN THERAPY: A COMPARATIVE STUDY

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ATTEMPTS to desensitize hay-fever patients by the use of oral antigen have been described by several observers. Touart,<sup>25</sup> in 1921, reported the relief of symptoms following the oral administration of 1/10 mg. daily doses of pollen. Thommen<sup>24</sup> later showed the variability in absorption and the need for larger doses when the antigen was given by this route. Black, in 1927 and 1928,<sup>3,4</sup> reported 150 cases in whom a 1/20 solution of antigen had been administered orally. He demonstrated the pollen factor in the blood, urine and stools, and pointed out the variability of absorption when the antigen was administered by mouth. Gatterdam,<sup>11</sup> in 1933 and 1934, told of the use of a pollen solution in pre-seasonal, coseasonal and symptomatic treatment, with fair results, and emphasized the difficulty in adjusting dosage.

Stier and Hollister,<sup>20</sup> in 1937, treated a large series of cases with oral pollen extract in various solutions, with a reported 79 per cent satisfactory results. McGrew,<sup>16</sup> in 1937, used a 1 per cent extract, while Rockwell,<sup>17</sup> in 1938, employed whole dried pollen antigen. Bohner<sup>6</sup> has reported a comparative series of oral pollen and parenterally administered pollen with comparable results. Bernstein<sup>2</sup> and Kirsner pointed out that though peptic digestion does not destroy the pollen antigen, yet the immediate absorption through the intestine is slight. Bernstein and Feinberg,<sup>2</sup> using a ragweed pollen extract, found it necessary to use 450 times as much orally as parenterally. They also estimated that the immediate absorption into the blood stream was only 1/4,000 of that following hypodermic injection.

During the past ten years conflicting statements and opinions as to effectiveness of oral pollen therapy have been published, with Zeller<sup>27</sup> condemning its use as a method of self-medication, and emphasizing the severe reaction attendant on its use. London,<sup>15</sup> however, held that patients who had severe reactions to parenteral injection never had any reaction to doses of pollen by mouth and that therefore the antigen was not absorbed. The latter also stated that combined oral and parenteral therapy gave no better or worse results than injection alone. Black,<sup>5</sup> about the same time, published an opposite opinion. Alperstein<sup>1</sup> is satisfied that enteral absorption occurs and found both reagin and allergin in blood of orally treated patients, but thinks the oral method of treatment less effective than the administration by injection. Swartz<sup>21</sup> however,

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TABLE I. ANALYSIS OF THERAPEUTIC RESULTS  
1937-1938

A				B				C			
Pollen, Orally				Pollen Parenterally				No Pollen			
Good	Fair	Questionable	None	Good	Fair	Questionable	None	Good	Fair	Questionable	None
6	3	1	1	5	4	1	0	0	0	3	7

feels that oral therapy is equally as effective as injection treatment. Feinberg, et al<sup>10</sup> have published conflicting reports.

At the present time nearly all workers appear to agree that pollen is absorbed enterally. It is also agreed that the rate and nature of this absorption are variable. This study is an attempt to evaluate critically, from a clinical point of view, the results of a method of oral pollen therapy.

Our interest in the use of oral antigens was aroused by the statements of patients that they were relieved from spring hay-fever symptoms by eating honey, or from the symptoms of ragweed hay fever by eating ragweed leaves. Because of this and because of the confusion over the relative absorption of antigen given orally as compared with that given parenterally we have given oral antigen to a small series of patients who have suffered from ragweed hay fever. At first, in 1936, we gave dried ragweed leaf powder in capsules. We were not satisfied with the use of leaf preparations in the experiment because of the difficulty of achieving adequate dosage and of the lack of definite relationship between the atopen in the leaf and in the pollen. Therefore, pure pollen preparations were used in 1937, 1938, 1939 and 1940. These consisted of capsules containing increasing doses of the mixed dried pollens of the spring and of the fall type. Some of this we made up; though most of it was furnished to us by the Eli Lilly Company.

Those patients who had asthma were omitted from this series the first two years because of the uncertainty of the results of the treatment. We also omitted those who had been treated previously by the subcutaneous method for more than one season, because of the possibility of residual benefits from previous therapy. All other patients were taken in rotation and placed in one of the following three groups:

*Group A.* These patients received oral pollen and a placebo of Coca's fluid, subcutaneously.

*Group B.* These patients received an oral placebo exactly similar in appearance to the capsule containing the oral pollens and a routine pollen extract, subcutaneously.

*Group C.* These patients received an oral placebo and Coca's fluid, subcutaneously.

TABLE II. ANALYSIS OF THERAPEUTIC RESULTS  
1938-1940

A				B			
Pollen Orally				Pollen Parenterally			
Good	Fair	Question- able	None	Good	Fair	Question- able	None
71	26	7	12	69	19	8	5

The groupings of all patients were changed each year; i.e., patients in Group A the first year who returned the second year were divided between Group B and Group C.

Results of therapy of all patients receiving adequate treatment and follow-up during the first two years of the study are shown in Table I.

The encouraging results of the first two years and the small number of patients studied prompted us to continue the work. During these years (1938 through 1940), only two groups were studied—Group A, receiving oral therapy; Group B, receiving parenteral therapy. The results of this study are shown in Table II, and the percentage interpretation of groups A and B of Tables I plus II are shown in Table III. Results were classified as *good*, *fair*, *questionable* and *none*. Patients were considered to have good results if they had less than a week's hay-fever or a very mild hay-fever during the mornings only for one or two weeks. They were considered to have fair results if they had a loss of the major symptoms and relief at night, and the season shortened by 50 per cent. They were considered to have questionable results if the patients themselves thought there had been improvement in spite of a continuation of symptoms. They were considered to have no results if neither patient nor doctor thought there had been improvement.

#### DISCUSSION

Maximum doses of 90,000 units were chosen arbitrarily the first two years. Some of our patients, however, received as much as 240,000 units every day while most were carried on 60,000 units twice a week. One of our patients on five different occasions developed asthma within two hours of taking 400 units by mouth while a dose of 200 units was well tolerated. Three patients developed general reaction with 15,000 units and were carried on a somewhat smaller dose. Several patients found the capsules mildly laxative. In six instances patients complained of abdominal pain of short duration within four hours of taking capsules. One patient not included in the series and previously treated for three years by the parenteral route with poor results, achieved 100 per cent relief with oral therapy used in connection with injections. In three cases combined oral and parenteral therapy increased the tolerated parenteral dose, and good results were obtained.

TABLE III. PERCENTAGE INTERPRETATION OF RESULTS  
GROUPS A AND B OF TABLES I AND II

Combined Groups A					Combined Groups B				
Pollen Orally					Pollen Parenterally				
Good	Fair	Question- able	None	Total Cases	Good	Fair	Question- able	None	Total Cases
77	29	8	13	127	74	23	9	5	111
60.6%	22.8%	6.3%	10.2%		66.6%	20.7%	8.1%	4.5%	

In our experience oral therapy presents the *disadvantages* of:

1. Greater cost of material. However, a shorter preseasonal treatment is needed and thus fewer visits are required.

2. Variability of dosage and difficulty of control do demand more time and care per visit on the part of the physician. No rigid plan of dosage is completely satisfactory and since dosage must be based mainly on subjective evidence, great care must be used in interviewing the patient. We have come to feel that there is considerable individual variability in absorption. Certainly, the conflicting reports in the literature of attempts to demonstrate the enteral absorption of pollen antigen bear this out.

3. Results in our hands are slightly less satisfactory than those achieved by parenteral injection.

There appear, however, certain *advantages*:

1. Absence of severe reaction and ease of administration. For patients who have had, and fear, severe reactions, or for those in whom fear of a "needle" is highly developed, these features are welcome.

2. The treatment also is more readily available, and for patients who must travel as well as for the large group of vacationists, oral therapy offers a happy solution. Great care must be exercised in training such patients to use the treatment intelligently so that both safety and good results are obtained. Some of the poorer results in our group of cases are in those patients who were given a supply of capsules and then for some reason were not seen for too long an interval.

3. Desensitization can be achieved in most cases much more rapidly by the oral method and it is certainly the method of choice for those patients presenting themselves shortly before their season starts.

4. Highly satisfactory results can be achieved with oral pollen therapy, when it is carefully administered.

#### CONCLUSION

1. Oral pollen therapy offers a satisfactory method of treatment of seasonal hay fever.
2. It requires careful administration and management, and is in no sense a satisfactory self-directed treatment.

3. Oral therapy has definite advantages of administration and convenience which make it the method of choice in treating some patients who have seasonal hay fever.

#### ADDENDUM

Since the completion of this study one of us (J. M. P.) has had occasion to use oral pollen in:

1. Eight cases previously treated unsuccessfully parenterally; with success in four patients.
2. Fifteen cases where because of travel, injections were impractical; with success in eleven patients.
3. Five cases in conjunction with parenteral administration where previous injection treatment alone was unsatisfactory; with four successful cases.

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## BENADRYL

### A Clinical Evaluation Based on One Hundred and Seventy-one Case Studies

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**B**ENADRYL, chemically known as Beta Dimethylaminoethyl Benzhydryl Ether Hydrochloride, was claimed to be a new antihistamine preparation which was synthesized and studied in the laboratories of Parke, Davis and Company.<sup>4,5</sup>

This drug was assigned to the Lancaster General Hospital for preliminary clinical investigation on October 2, 1945.\* Pharmacologically, the drug was claimed to have the ability to neutralize or counteract the effects of histamine. Experiments conducted on animals revealed that benadryl is fifteen to twenty times more active than aminophyllin experimentally in relieving bronchial constriction caused by histamine injection.<sup>4,5</sup>

The effect of benadryl was compared to that of papaverine. It was found to be 650 times as effective in antagonizing histamine; fifty times as effective in antagonizing acetylcholine.<sup>3,4</sup> Most investigators now agree that benadryl exerts a threefold action; first, an antihistamine action; second, an antispasmodic action; and third, an atropine-like effect.<sup>3,4</sup> This study has also convinced the author that the drug has a fourth effect, that of central nervous system depression.

Horton<sup>6</sup> has long been of the opinion that a common denominator exists in all allergic diseases (such as hay fever, asthma, urticaria, angioneurotic edema, migraine, et cetera) and also in some diseases that at the present time are not classified as allergic in origin. He states that the common denominator is edema which is provoked by the release of histamine or a histamine-like substance into the blood. The response produced by the release of histamine or the histamine-like substance can be either general or local.

Our assigned problem was to evaluate clinically the effect of benadryl on patients suffering from long-standing, recurrent, intractable asthma, chronic urticaria, recurrent migraine and any other conditions thought to be allergic in origin. If the etiology in all of the above-mentioned states is common, then treatment with a drug which has an antihistamine action could be easily evaluated.

This study covers a total of 171 cases. Similar cases are grouped as follows:

1. (a) Hay fever—32 cases. No previous treatment.
- (b) Hay fever—44 cases. Previously treated with specific pollen antigens.

\*Benadryl was donated through the courtesy of Mr. Owen J. Rowlands of Parke, Davis and Company.

2. Intractable asthma, severe—21 cases.
3. (a) Chronic urticaria—21 cases.  
(b) Acute urticaria—28 cases.
4. Migraine—3 cases.
5. Atopic dermatitis—7 cases.
6. Erythema nodosum—1 case.
7. Perennial vasomotor rhinitis—11 cases.
8. Sea or motion sickness—2 cases.
9. Dysmenorrhea—1 case.

1. (a) *Hay fever—32 cases, no previous treatment.*—These patients all had typical symptoms, such as epiphora, lacrymation, sneezing, itching of the nose, rhinorrhea, congestion of the nasal mucous membrane accompanied by blocking, itching of the palate, coughing, et cetera. None of these patients had had previous desensitization therapy. The average dose of benadryl administered was 250 mg. per day, by the oral route. Six of this group of patients were completely relieved by the drug. These patients could not be classified as severe hay-fever sufferers. Twenty-six were relieved from 30 to 55 per cent. The amount of relief that they obtained was directly related to the pollen count. If the count was high, the patients' symptoms were more severe. A number of these patients experienced side reactions consisting of mild nausea, occasional vomiting, dizziness, generalized tingling, drowsiness, extreme in some cases, and a mild feeling of weakness. A number of these patients voluntarily increased the amount of benadryl they were taking as the severity of their symptoms increased. The side reactions were probably precipitated by the increased dosage. Five patients also complained of dryness of the mouth and mild difficulty in swallowing. In the six patients who received complete relief and in the twenty-six patients who received from 30 to 55 per cent relief, the dosage of the drug was gradually reduced to determine the minimum effective level of the drug necessary for relief. The amount of benadryl taken orally in the last-mentioned two groups was cut to between 125 mg. and 200 mg. daily. This was accomplished by giving each patient 25 mg. and 50 mg. capsules, with instructions to take 25 mg. q.i.d., if their symptoms were not severe, and 50 mg. q.i.d., if their symptoms were severe.

1. (b) *Hay fever—44 cases. Previously treated with specific pollen antigens.*—In this group of patients benadryl was used as an adjuvant. The patients were specifically instructed not to take the drug unless symptoms of hay fever were present. During the past fall, the pollen count in this area was extremely heavy between September 8 and September 24, 1946. Nineteen of this group of forty-four patients used benadryl during this period of time to provide symptomatic relief. Small doses of benadryl relieved most of these people. The average dose ranged between 25 mg.

t.i.d. and 50 mg. t.i.d. A number of other patients also seemed to tolerate pollen therapy much better. In this group of patients specific desensitization treatment plus benadryl when necessary to relieve symptoms when present provided relief in from 70 to 85 per cent of the cases.

2. *Intractable asthma, severe—21 cases.*—From 100 mg. to 400 mg. of the drug was used per day by means of the oral route. Fourteen (two-thirds) of these patients obtained no relief from the drug after taking the medication for three days or more. Five patients were definitely made worse by the drug. Two experienced hallucinations and extreme drowsiness after taking between 300 mg. and 400 mg. of the drug orally for a period of five days. On these two patients other methods of therapy were tried. The severe attack from which one of these patients was suffering, was finally relieved by the use of  $7\frac{1}{2}$  gr. aminophyllin in 50 c.c. of glucose every four hours intravenously. Oxygen and helium were also used on this patient, along with mechanical aspiration of the mucus that accumulated in the mouth and throat. No form of epinephrine was effective. This was also observed in other patients. The probability exists that benadryl may in some way counteract or neutralize the effect of epinephrine. The other patient's attack was not relieved by any form of therapy used. He died suddenly from what was thought to be a respiratory failure. It was found at postmortem examination that he had a pulmonary emphysema and hypertrophy and dilatation of his right auricle and ventricle. The examination revealed a chronic bronchitis, pneumonitis, pleuritis, fibrosis and pleural adhesions, and a slight nephrosclerosis of the arteriole type. There was no evidence of any acute or chronic degenerative changes that may have resulted from the ingestion of benadryl.

Another one of this group of five patients also died. Postmortem examination\* revealed hypertrophy of the right auricle and ventricle. There was marked pulmonary edema, bilateral bronchopneumonia and a thrombosis of one of the pulmonary vessels with multiple small infarcts and passive congestion of the liver. The terminal portion of the duodenum showed central necrosis and erosion. There was no evidence of any toxic degeneration of the organs which may have been caused by the ingestion of benadryl.

Seven patients (one-third) derived some improvement following the ingestion of benadryl. Their attacks were less, more infrequent and they were more relaxed and slept better. Some of the patients in this group thought they were receiving sedation. Two of the patients compared the action of benadryl to that of triple bromides.

3. (a) *Chronic urticaria—21 cases.*—Here the results were excellent. The typical urticarial lesions would disappear shortly after preliminary in-

\*Postmortem examinations performed by Dr. Thelma Boughton, Pathologist, Lancaster General Hospital, Lancaster, Pa.

gestion of from 50 mg. to 100 mg. of the drug. The average dose necessary to keep the patient free from lesions ranged from 25 mg. q.i.d. to 50 mg. q.i.d. It is well known that chronic urticaria has long been a troublesome problem and still remains so. The itching, insomnia, pain, nervousness and other symptoms that accompany chronic urticaria are quite annoying. The condition at times is very dangerous if localized edema occurs in the larynx, trachea or pharynx. Many forms of therapy have been employed to give these sufferers even short periods of freedom from symptoms. The relief obtained by these patients following benadryl therapy was so striking and complete that the drug will probably be the one of choice in the treatment of chronic urticaria in the future. This statement is made in spite of the fact that a large number of patients experienced drowsiness after the ingestion of the drug. Three of the patients in this group also complained of inability to concentrate and co-ordinate properly after taking the drug over a period of time. Prompt recurrence of the urticaria took place in practically the entire group of patients when benadryl was temporarily discontinued.

Therefore, diagnostically, the physician must try to determine the etiology of the urticaria. This sometimes can be accomplished by skin testing or by careful history taking; however, if the specific reagins are absent in the blood stream, skin tests give the investigator no information. Curtis and Owens<sup>1</sup> first reported the use of benadryl in the treatment of acute and chronic urticaria. Later P. A. O'Leary and E. M. Farber<sup>7</sup> also published a paper on the same subject. Their reports were enthusiastic.

3. (b) *Acute urticaria*—28 cases.—Nineteen of these patients experienced almost immediate relief after benadryl therapy was instituted. The itching and nervousness from which they suffered usually disappeared about four hours after benadryl therapy was begun. Five of this group of patients also improved, even though their lesions did not completely disappear. It was necessary to discontinue the use of benadryl in the remaining four members of this group because of the appearance of extremely severe, so-called, side chain reactions, consisting of nausea, dizziness, blurring of vision and extreme drowsiness.

4. *Migraine*—3 cases.—None of these patients obtained any relief following treatment with benadryl. One patient, a sufferer of long standing, then decided to take 150 mg. of the drug as soon as his symptoms started. He obtained no relief, even though he repeated the dose several times after his symptoms appeared. He developed side reactions such as vomiting, dizziness, dryness of tongue, difficulty in swallowing and some blurring of vision.

5. *Atopic dermatitis*—7 cases.—All members of this group of patients were less than six years old. The dose of benadryl ranged from 12½ mg.

q.i.d. to 25 mg. q.i.d. and the average duration of therapy was eleven days. There was some slight improvement in two of the cases. I attribute this improvement to a diminution of the itch reflex. None of the cases cleared.

6. *Erythema nodosum*—1 case.—This patient was given 50 mg. of the drug four times daily. He experienced no relief after taking the drug for a period of four days. He also experienced no side reactions.

7. *Perennial vasomotor rhinitis*—11 cases.—Nasal discharge, sneeze reflex, itching of the nose were all reduced in seven of this group. The other four patients received no relief from the drug. The dose of benadryl used ranged from 25 mg. q.i.d. to 50 mg. every four hours. Seven patients obtained relief from the ingestion of the drug. They immediately experienced remissions if they discontinued its use.

8. *Sea or motion sickness*—2 cases.—The author was one subject and a fellow physician was the other. Neither of us obtained relief. The author experienced extremely severe side reactions such as nausea, dizziness, vomiting, tingling and blurring of vision. However, in all fairness, it must be stated that movement of the boat was probably responsible for many of these symptoms, and this report is by no means conclusive.

9. *Dysmenorrhea*—1 case.—This patient took 50 mg. of the drug every four hours for a period of three days without relief. In studying this group of patients, the author noticed that the two most frequent side reactions were nausea and drowsiness. All of us occasionally have to deal with troublesome insomniacs. Benadryl was used by one such patient. He was instructed to take 100 mg. of the drug at 4:00 p.m. and another 100 mg. at 8:00 p.m. He experienced complete relaxation for the first time in several years and was able to obtain a complete night's rest. This patient is also more relaxed during the day and is able to do his work in a more efficient manner. This experience has further convinced the author that benadryl has a depressant effect on the central nervous system. Further trial in conditions of this kind is indicated.

#### CONCLUSION

1. Loew and his associates had tested the toxicity of benadryl in rats and guinea pigs and found it to be low.

2. Curtis and Owens first used the drug on human beings. They noticed the drug had a wide margin of safety.

3. Benadryl is a very useful addition to our therapeutic armamentarium, especially in the following conditions: acute and chronic urticaria, hay fever, and perennial vasomotor rhinitis. It is also of limited value in some cases of intractable asthma.

4. The extent and method by which the drug interferes or neutralizes histamine is still not known. Further study is indicated.

5. The drug very definitely seems to have a sedative effect. Benadryl seems to counteract and neutralize the effect of adrenalin or epinephrine. Benadryl very definitely does not relieve the majority of asthmatics studied; it proved of no value in the treatment of migraine, seasickness, dysmenorrhea, and one case of erythema nodosum. It proved of little value in the treatment of atopic eczema.

6. Careful allergy studies should be conducted on all allergic persons to determine the etiology of the condition from which the patient is suffering. Elimination of the cause or focus of infection and careful desensitization treatment, if indicated, is still the best procedure. Benadryl can be used to provide symptomatic relief in those conditions in which it is effective. It should not be used indiscriminately, as it produces serious side reactions.

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#### ASTHMA IN THE NEWBORN

In the July-August issue of the *Hawaiian Medical Journal*, F. D. Nance reports seven cases, which came under his observation and which illustrate the following points.

1. Asthma in the newborn is not uncommon, but is probably the most frequent cause of a wheeze in these infants.
2. It is almost always dietary in origin.
3. Since the diet at this age is extremely limited, the detection of the offending food is simple.

The author concludes that the history that an infant wheezed since birth plus the finding of an expiratory wheeze should suggest a probable diagnosis of asthma due to food allergy. Physicians should be unwilling to accept a diagnosis of thymus enlargement as the cause of noisy respiration in the newborn on the basis of roentgen observations alone.

# KAPOSÍ'S VARICELLIFORM ERUPTION

## Relation to Atopic Dermatitis

By LEON UNGER, M.D., F.A.C.A.

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**DEFINITION:** Kaposi's varicelliform eruption is a rather rare condition which is now acceptable as a distinct disease entity. It is characterized by a stormy onset with high fever, prostration, nausea, vomiting, diarrhea, and signs of kidney irritation. The rash is almost entirely localized to parts of the skin previously affected by a chronic dermatitis, usually allergic or atopic; vesicles and pustules with umbilication are typical.

### CASE REPORT

Miss N. J., aged nineteen years, a school teacher, was admitted to Wesley Memorial Hospital at 3:00 A.M., September 4, 1944, acutely ill, with high fever. She developed a sore throat five days previously, and a physician prescribed a sulfa tablet every three hours. A papular rash began on the body and spread to the arms, face, neck and upper part of the back. The drug was stopped after two days. Fever, prostration, nausea, vomiting, bloody diarrhea, and hematuria soon followed, and the eruption spread rapidly and became vesicular. Pruritis was not a complaint. The temperature was 104° F. the day before admission.

She had been under treatment by another physician for about eight or nine years for hay fever and severe flexural "eczema" (atopic dermatitis), especially affecting the bends of the elbows and sides of the neck. She had been found allergic to many foods and pollens. The previous history was otherwise not noteworthy. She had an old vaccination scar.

*Examination.*—She was a well-nourished white woman with the deeply pigmented, hyperkeratotic skin of her neck swollen and oozing, and with many unbroken vesicles, most of which were umbilicated. Lesions were also present on the face, neck, arms, upper chest, and in the groins. The palms, soles and mucous membranes were not involved. The individual lesions were from 5 to 7 mm. in diameter, thick walled, and pearly in appearance. There was no surrounding erythematous aerola or scratch marks. New lesions appeared for several days. Much pain occurred in turning the head from side to side (Fig. 1).

Stupor was present on admission, and the fever reached 105° F., with a pulse rate of 126 on September 6, two days after admission and seven days after the onset of illness. Delirium and involuntary urination occurred, and the temperature remained high for two more days; it then returned to normal rather rapidly (Fig. 2). The entire duration of fever was about eleven days. As the fever began to recede, the mental condition improved, as well as the general appearance, and the rash began to fade. At the time of discharge, September 17, the vesicles were gone, the skin was stained, without scars, but the previously lichenified flexural dermatitis was still present.

Physical examination was otherwise practically normal. The pharynx was red; no pulmonary, cardiac, abdominal nor pelvic abnormalities were found.

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Dr. Unger is attending physician of Wesley Memorial and Cook County Hospitals, Chicago. The author acknowledges, with gratitude, the aid of Arthur William Stillians, M.D., and Michael Higgins Ebert, M.D.

## KAPOSI'S VARICELLIFORM ERUPTION—UNGER

*Laboratory findings.*—The urine, of which only 2,250 c.c. were excreted one day despite an oral and intravenous intake of 4,950 c.c., contained 50 to 100 mg. of albumin per 100 cubic centimeters, but no blood nor casts. The blood contained 4,080,000 red cells with some anisocytosis and polychromasia, 13 grams (83 per cent)



Fig. 1. N. J., aged nineteen years, with marked umbilicated vesiculopustular eruption superimposed on sites of previous atopic dermatitis; high fever and prostration associated.

of hemoglobin, and 11,400 and 11,850 white corpuscles, of which 88 per cent were polymorphonuclear leukocytes, 10 per cent lymphocytes, 1 per cent basophiles, and 1 per cent monocytes. Despite the underlying allergic condition, eosinophiles were not found (a common occurrence in allergic individuals who suffer from some superimposed, nonallergic disease). Toxic granulation of the neutrophils was found. The Kahn and Wassermann tests were negative; the carbon dioxide combining power was 34.9 volumes per cent; the serum total protein was 5.31, with albumin 3.1 and globulin 2.21. Culture of the blood gave no growth, but culture of the contents of a vesicle yielded a heavy growth of hemolytic *Staphylococcus albus*. No parasites were found in the feces.

The local treatment consisted of cool dressings of 6 per cent aluminum subacetate solution until the fever disappeared; then an ointment of borated petrolatum, 10 per cent. A boric acid lotion was used to irrigate the conjunctival sacs. The treatment was otherwise symptomatic, with main emphasis on large intake of fluid, much of which was administered intravenously.

At first there was some doubt as to the diagnosis, chiefly because of the possibility of a sulfonamide reaction, but the correct diagnosis was suggested by Dr. Stillians, consultant.

Dr. Ebert isolated the virus of herpes simplex from one of the vesicles by injecting the material into a rabbit's cornea, but lost the virus in transmission experiments.

### ETIOLOGY OF KAPOSI'S VARICELLIFORM ERUPTION

In 1887 Kaposi<sup>18</sup> described a new disease which was an alarming complication of "eczema infantum." The vesicles were described as lentil-sized, "filled with a clear serum, and the majority umbilicated." Kaposi



# KAPOSI'S VARICELLIFORM ERUPTION—UNGER

called this eruption "varicelliform," but stated that the term "eczema herpetiforme" is also correct.

Since this work there has been a controversy among dermatologists

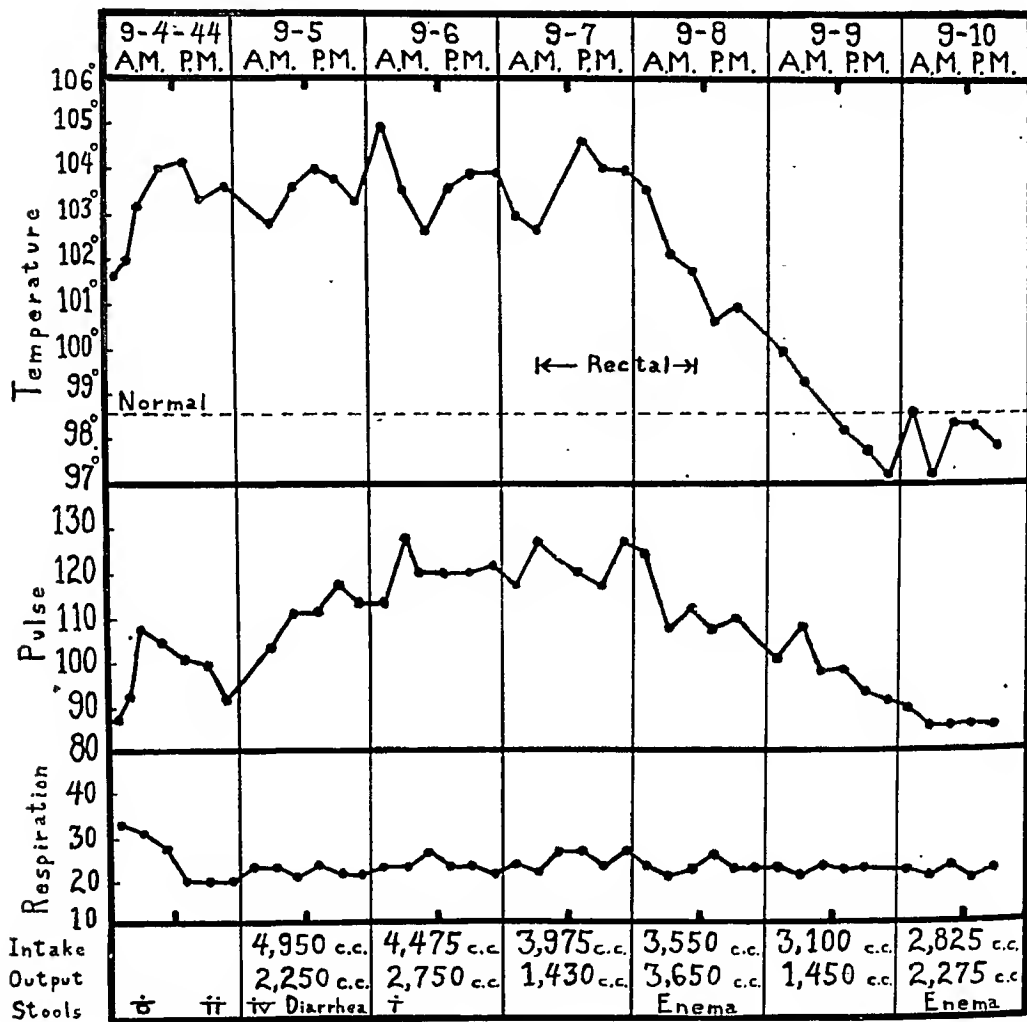


Fig. 2. Temperature, pulse and other data during height of attack.

concerning the relation of this disease to vaccinia accidentally superimposed on infantile eczema. Both occur only upon already inflamed skin, and both have lesions resembling those of smallpox (variola). This controversy has now been settled by the discovery of Seidenberg,<sup>28</sup> who showed that the virus of herpes simplex is the causative agent of Kaposi's varicelliform eruption and that it has no relation to vaccinia.

This discovery has been amply verified by Wenner,<sup>31</sup> Heilman in a case reported by Barton and Brunsting,<sup>1</sup> Blattner and Heys, reported by Lane and Herold,<sup>21</sup> and by Lynch and co-workers.<sup>22</sup> Further confirmation comes from the recent article by Blattner, Heys, and Harrison.<sup>5</sup> These authors isolated a filterable virus of the herpes group from fluid removed from cutaneous vesicles on the fifth and sixth days of illness. The patient

## KAPOSI'S VARICELLIFORM ERUPTION—UNGER

was a fifteen-month-old white baby boy who had had atopic eczema since the age of six weeks and who then developed an acute exanthem, with high fever and leukopenia. The patient recovered and left the hospital in fourteen days; the acute lesions completely disappeared, and the infantile eczema was less marked than it had been for a long time. "The virus was isolated not only by means of the rabbit's cornea but also directly on the chorioallantois of the developing hen's egg. The latter finding would seem to exclude any possibility that a latent herpes virus might have been reactivated in the rabbit by experimental manipulation." Kaposi's varicelliform eruption is therefore almost certainly due to a virus of the herpes simplex group; it is not related to vaccinia.

Lynch<sup>22</sup> points out the difficulty in isolating the virus, which must be sought from unruptured vesicles, "preferably not over one or two days old. For these reasons it is likely that the diagnosis of herpetic complication of eczema will usually be made on a clinical basis. The pathogenesis seems to be well established, and it is now only necessary for clinicians to become familiar with the disease."

Staphylococci and streptococci have been isolated by many observers (we isolated hemolytic *Staphylococcus albus*). But these bacteria are apparently secondary invaders.

Other articles concern this condition and the heretofore confusing vaccinia superimposed on eczema. Some of the authors are Juliusberg,<sup>18</sup> Ellis,<sup>11</sup> Corson and Ludy,<sup>10</sup> Goeckerman and Wilhelm,<sup>16</sup> MacLachlan and Gillespie,<sup>23</sup> Tedder,<sup>30</sup> Schwartz,<sup>27</sup> King,<sup>20</sup> Ronchese,<sup>26</sup> Brown,<sup>8</sup> Freud,<sup>12</sup> Freund,<sup>13</sup> Frühwald,<sup>14</sup> Bentley,<sup>2</sup> Platou,<sup>25</sup> Brain and Lewis,<sup>7</sup> Strickler,<sup>20</sup> Blattner, Heys and Harrison,<sup>4</sup> Blattner, Heys and Gollub,<sup>3</sup> Hershey and Smith,<sup>17</sup> Connor and Gonce,<sup>9</sup> Wise and Sulzberger,<sup>32</sup> and Pepple, Murrell and Fowlkes.<sup>24</sup>

The *incidence* of the disease seems to be on the increase. At least thirteen cases have been listed from the Mississippi Valley region within the past three years. The total number of cases is unknown as many are not reported, but probably almost a hundred have occurred.

*Predisposing cause.*—Almost every case has occurred in a patient who already had a skin disease. Of sixty-seven cases reported by Barton and Brunsting<sup>1</sup> in 1944, fifty-three (79 per cent) had atopic dermatitis (allergic eczema, neurodermatitis). This high percentage is very important to allergists and dermatologists as it indicates the danger which may befall patients with "eczema" from contact with a virus disease such as herpes simplex. Seborrheic dermatitis occurred in thirteen patients, and impetigo in thirteen patients. Scabies, sycosis vulgaris, and simple trauma may also precede the varicelliform eruption. Of the fifty patients for whom the sex was listed, thirty were males, twenty females. Children three years old or younger were affected in fifty-one of these sixty-seven cases, with only thirteen patients over fourteen years of age. Small epi-

demics have occurred, as Kaposi<sup>19</sup> saw ten cases within a short period, and McLachlan and Gillespie<sup>23</sup> found sixteen cases in a British hospital for children. These groups suggest that an increase of virulence of the virus occurs at times.

#### SYMPTOMATOLOGY AND DIAGNOSIS

The main findings are sudden onset with prostration, fever, nausea, vomiting, diarrhea, and the typical rash, as already mentioned. The onset is usually sudden with a quick rise in temperature to 103° to 105°; the temperature usually remains high for several days, then drops by lysis. The pulse is rapid with the fever. Prostration and stupor are common, as in our case, and delirium and mental confusion are frequent. Death may follow.

The rash itself is typical. Many of the lesions are umbilicated vesicles which become pustular, with new lesions appearing for several days. They heal with little or no scarring. The lesions usually appear on skin which is already affected by some form of dermatitis, especially that of the atopic type. Regional lymphadenitis is also present, especially cervical.

Complications have been noted, e.g., anuria, otitis media, purulent rhinitis, conjunctivitis, and occasionally severe infections of the regional lymph nodes. Involvement of the mucous membranes is uncommon.

Moderate increase in leukocytes is usual. Albumin and casts may occur in the urine, and melena is not uncommon.

The finding of the herpes-like virus confirms the diagnosis, but the clinical findings themselves are diagnostic.

#### DIFFERENTIAL DIAGNOSIS

Other conditions in which vesicles and pustules occur and all causes of prostration and fever must be ruled out. Variola, eczema vaccinatum, varicella, drug eruptions, impetigo, herpes zoster, and secondary pyogenic infection in a patient with eczema are especially important.

From *variola* the disease can be distinguished by the absence of a prodromal period of about three days, the failure of the symptoms and fever to subside on appearance of the eruption and to recur about the eighth day, and the recurrence of vesicles for a week or ten days. Variola also tends to involve the hands and soles, a finding usually absent in Kaposi's condition. The presence of a good vaccination mark in a severe case previously afflicted with chronic dermatitis also speaks against the diagnosis of variola.

The differentiation from *eczema vaccinatum*, vaccinia inoculated upon a pre-existing dermatitis, is difficult. A history of exposure to cowpox vaccine and the absence of a vaccination scar favor the diagnosis of vaccinia, but this condition usually spreads rapidly over most of the body. Kaposi's varicelliform eruption, on the other hand, usually symmetrically involves the upper half of the body. Identification of the virus may be

necessary before a decision can be reached; as already pointed out the viruses of the two conditions are not related. Vaccinia is a serious condition with a high mortality. Vaccination of persons with dermatitis is extremely dangerous, and patients with dermatitis must avoid recently vaccinated individuals and vaccinia unless they themselves have been immunized by previous vaccination. Glaser<sup>15</sup> has seen at least six cases of eczema vaccinatum.

From *varicella* all except the mildest examples of Kaposi's eruption are distinguished by the frequent involvement of the face, the tendency to confluence of the eruption upon pre-existing areas of dermatitis, especially the sides of the neck, and the stormy onset and course.

*Drug eruptions* may confuse. In this case, sensitization to sulfonamide drug was at first suspected because the condition occurred very quickly after the drug was administered. But drug rashes are not restricted to pre-existing areas of dermatitis, nor do they exhibit the typical umbilicated type of eruption. The clinical course is also different.

In *impetigo* the variation in the size of the lesions, their fragility, asymmetry, and lack of definite and regular umbilication distinguish it from the varicelliform eruption. Impetigo is not self-limited, and seldom attacks with such ferocity except in young infants; leukocytosis usually accompanies these very rare severe episodes.

In *herpes zoster*, even in the rare disseminated form, there should be some unilateral predilection, with smaller groups of lesions, not often upon a previously inflamed skin. Pain often precedes the eruption, and fever is uncommon. The lesions are not definitely umbilicated.

*Secondary pyogenic infections* occasionally occur in eczema. Fever, leukocytosis and prostration may be severe in infants, but the characteristic thick-roofed vesiculo-pustular eruption does not occur. Boisveit and Powers<sup>6</sup> state that atopic dermatitis and streptococcal fever (rhinopharyngitis, cervical adenitis, low-grade fever of several weeks' duration) are common diseases in the first three years of life.

#### PROGNOSIS

The general practitioner, as well as the pediatrician, dermatologist, and allergist, should be on the lookout for this varicelliform eruption. It has a considerable mortality which, according to Barton and Brunsting,<sup>1</sup> amounts to 27 per cent in infants under three, and to more than 15 per cent in adults. One has only to see one case to realize the extreme prostration and danger.

#### TREATMENT

This may well be divided into *prophylactic* and *active*; the former is important. Individuals with eczema or other dermatological conditions should rigidly avoid virus conditions, especially simple cold sores (*herpes simplex*). A mother or nurse who has one of these virus diseases must

not contact infants and children who have a skin disease. The attending physician should point out these dangers. Allergists in particular should acquaint themselves with this disease.

Active treatment to date is chiefly symptomatic. Local measures vary. Cool dressings of 6 per cent aluminum subacetate solution may be applied while fever exists; borated petrolatum, 10 per cent, may then be used. The usual measures given for prostration and feverish conditions are necessary, especially fluids given orally, intravenously, subcutaneously, and/or rectally, as the emergency requires. Sulfonamide therapy has been praised by Connor and Gonce,<sup>9</sup> who obtained good results in two of their three patients, but Lane and Herold<sup>21</sup> observed a dangerous leukopenia in one case.

Lynch<sup>22</sup> has suggested that pooled serum or plasma of adults contains sufficient antibody to be of service in combating the effects of the virus of herpes simplex. This therapy may well be effective in the treatment of the varicelliform disease and eczema vaccinatum, both dangerous, both virus diseases, though not related.

#### SUMMARY AND CONCLUSIONS

1. Kaposi's varicelliform eruption occurred in a young woman with previous atopic dermatitis (eczema). Recovery occurred after a stormy course with prostration, high fever, and typical vesiculopustular umbilicated lesions.

2. The condition has been definitely proved to be due to a virus of the herpes simplex group which infects individuals with previous skin disease, especially atopic dermatitis.

3. The virus of the varicelliform condition is not related to that which causes eczema vaccinatum.

4. The etiology, symptomatology, diagnosis, differential diagnosis, prognosis, and treatment are outlined.

5. Physicians should warn individuals with eczema or other dermatological conditions to avoid persons who have herpes simplex because of the danger of developing Kaposi's varicelliform eruption.

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## INSUFFLATION OF SULFONAMIDE DRUGS

"Sensitivity from Insufflation of Powdered Sulfonamide Compounds in Acute Infections of Nose and Throat" is the title of a paper by H. C. Ballenger, M.D., published in the July, 1947, issue of *Anesthesiology*.

Ballenger applied sulfathiazole, sulfanilamide and sulfadiazine powders, alone or in combination, by insufflation to the mucous membrane of the upper respiratory tract in 1,500 patients with various acute infections of the nose and throat. Six thousand applications were made during a three-year period from July 1, 1943 to July 1, 1946. An average of about 2.5 treatments were given for each acute attack. Many of the patients have had two, three or more attacks during the three-year period. The sore throat and inflammation, especially that of the palate, nasopharynx and pharynx, were frequently stopped within twenty-four hours. The rhinitis and

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# MOLD FUNGI IN THE ETIOLOGY OF RESPIRATORY ALLERGIC DISEASES

## V. Further Studies with Mold Extracts

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A MAJOR activity of the Association of Allergists for Mycological Investigations continues to be the study of various methods of preparation of mold extracts. Reports<sup>2,4</sup> in 1944 described the preparation of four experimental extracts and the results of skin testing with these antigens. Pellicles of *Alternaria tenuis* and *Aspergillus niger* used in these studies were subjected to twenty washings with normal saline, then were modified further for extraction as follows:

Method 1—Dried only by lyophilization.

Method 2—Dried by lyophilization, defatted.

Method 3—Dried by lyophilization, defatted, ground.

Method 4—Dried by lyophilization, ground.

Method 5—"Usual Method" (dried slowly).

Intradermal skin tests with dilutions of 1:1,000 failed to elicit any significant difference between any of the experimental extracts and extracts prepared by our "usual method" (No. 5). In none of these extracts could histamine or a histamine-like substance be detected to account for any irritating properties which the extracts might possess.<sup>6</sup> It was, therefore, concluded that our acknowledged<sup>1</sup> lack of reliable extracts was based upon insufficient concentration of the active substance rather than upon nonspecific irritating properties. Finally, a study of the pellicle washings and of the broth in which the pellicles were grown revealed the presence of skin-reacting substances, not only in the broth but also in the washings, when tested on *Alternaria*-sensitive patients (5); this was correlated with an absence of histamine or histamine-like substance.<sup>6</sup>

### EXPERIMENTAL EXTRACTS 6 TO 12

In order to continue the study of various methods of extraction, more extracts were prepared in the summer of 1944 from the same two molds, *Alternaria tenuis* and *Aspergillus niger*. The pellicles were separated as thoroughly as possible from the broth by decanting and filtration, cut into thin strips, and, without any washing, were frozen immediately between

From the Department of Botany and Bacteriology, The University of Texas, in collaboration with the Association of Allergists for Mycological Investigations. Assisted by a Grant in Aid from the Alumni Research Fund of the Society of the Sigma Xi. Read in part before the Association of Allergists for Mycological Investigations, Pittsburgh, Pennsylvania, January 19, 1945, and in part at a meeting of the same group, San Francisco, California, June 28, 1946.

cakes of dry ice, then dried by lyophilization. A portion of the lyophilized pellicle was mixed in a Waring Blendor with Hollister-Stier solution in a ratio of 1:20 and, after extracting in the refrigerator for forty-two hours, was sterilized by Seitz filtration. Another portion of the lyophilized pellicle was defatted in Soxhlet equipment with ethyl ether, after which it was extracted similarly. The broth which had been freed of all pellicle and spores was lyophilized. This was accomplished easily with the *Aspergillus* broth, but with *Alternaria* broth a certain amount of gummy residue could not be avoided. The lyophilized broth was redissolved in Hollister-Stier solution in ratio of 1:10, based on the dried broth.

An effort was made by one of us (Tatge) to separate the protein molecule into large and small molecular aggregates by dialysis, in order to obtain a potent skin-reacting fraction that would produce specific whealing, lessen the incidence of nonspecific reaction, and cause no constitutional reaction when used intradermally for diagnosis only.

It had been shown by Johnson and Rappaport<sup>3</sup> that ragweed pollen extract could be split by dialysis into at least two fractions, the dialysate containing a highly skin-reactive aggregate and the semipermeable membrane retaining an antigenic fraction, possibly of lower skin reactivity.

On this basis, work was begun on *Alternaria tenuis* pellicle, *Alternaria tenuis* broth, *Aspergillus niger* pellicle, and *Aspergillus niger* broth. Pellicles and broth were separated and the unwashed pellicles were dried completely in an air-conditioned drier, then ground to a powder in the ball mill. The powdered pellicles were extracted in distilled water in 1:20 ratio and this extract dialysed in a cellophane bag against an equal volume of water for forty-eight hours. The dialysate labeled small aggregate and the bag contents labeled large aggregate were placed in evaporating dishes and concentrated in the drier with a continuous stream of warm air (80° F.). The residue of the small molecular fraction was gummy, but that of the large molecular fraction was drier and less gummy. Each fraction then was dissolved in Hollister-Stier solution in 1:20 ratio and sterilized by Seitz filtration. From the broths similar extracts were prepared.

With *Alternaria*, it was found that unless the cellophane bag was changed at the end of twenty-four hours it would disintegrate. Similar enzyme activity has been noted in other experiments involving *Alternaria* pellicle extract and broth, but it has not been observed with *Aspergillus niger*.

In order to minimize the influence of aging, all the extracts were prepared as nearly simultaneously as possible. These extracts were labeled only with serial numbers 6 to 12 and were distributed to our membership for skin testing. For comparison, an extract freshly prepared according to our "usual method" (5) was included. To recapitulate, these extracts were prepared as follows:



TABLE I

METHOD	ALTERNARIA TENUIIS BC 17					ASPERGILLUS NIGER BC 70				
	Intradermal Tests				Scratch	Intradermal Tests				Scratch
	1:100,000	1:10,000	1:1,000	1:100		1:100,000	1:10,000	1:1,000	1:100	1:20
"Usual" No. 5 Washed, slowly dried pellicles	Cases tested 19	Cases tested 27	Cases tested 29	Cases tested 24	Cases tested 18	Cases tested 18	Cases tested 18	Cases tested 18	Cases tested 18	Cases tested 17
	Reactions 32%	Reactions 48%	Reactions 69%	Reactions 100%	Reactions 39%	Reactions 0	Reactions 6%	Reactions 11%	Reactions 39%	Reactions 18%
No. 6 Unwashed, lyophilized pellicles	Cases tested 18	Cases tested 26	Cases tested 29	Cases tested 23	Cases tested 18	Cases tested 18	Cases tested 18	Cases tested 18	Cases tested 18	Cases tested 17
	Reactions 28%	Reactions 58%	Reactions 76%	Reactions 96%	Reactions 28%	Reactions 0	Reactions 6%	Reactions 11%	Reactions 67%	Reactions 24%
No. 7 Unwashed, lyophilized, defatted pellicles	Cases tested 18	Cases tested 26	Cases tested 29	Cases tested 24	Cases tested 18	Cases tested 18	Cases tested 18	Cases tested 18	Cases tested 18	Cases tested 17
	Reactions 28%	Reactions 54%	Reactions 76%	Reactions 100%	Reactions 28%	Reactions 0	Reactions 6%	Reactions 22%	Reactions 50%	Reactions 18%
No. 8 Broth	Cases tested 19	Cases tested 27	Cases tested 29	Cases tested 24	Cases tested 18	Cases tested 18	Cases tested 18	Cases tested 18	Cases tested 18	Cases tested 17
	Reactions 53%	Reactions 67%	Reactions 86%	Reactions 100%	Reactions 50%	Reactions 0	Reactions 17%	Reactions 33%	Reactions 83%	Reactions 12%

Members performing the studies from which above data taken:

Dr. Sam Sanders  
Dr. Edw. George Tatge  
Dr. F. W. Wittieh  
Dr. Homer E. Prince

- Method 5—"Usual method" (washed, slowly dried pellicle).  
 Method 6—Unwashed pellicle, lyophilized.  
 Method 7—Unwashed pellicle, lyophilized, defatted.  
 Method 8—Broth.  
 Method 9—Unwashed pellicle, "small aggregate" (dialysate).  
 Method 10—Unwashed pellicle, "large aggregate" (bag contents).  
 Method 11—Broth, "small aggregate" (dialysate).  
 Method 12—Broth, "large aggregate" (bag contents).

The results of skin testing on twenty-nine patients are shown in Table I. In all the patients, molds were considered by the investigators to be major allergens; *Alternaria* was specified in twenty patients and implied in the remaining nine. On the other hand, *Aspergillus niger* was not specified once as a major allergen, even though the investigators also tested eighteen of the patients with this mold. In the tests with *Alternaria tenuis*, there did not seem to be any significant difference in the reactivity of preparations 5, 6, and 7, all of which were pellicle extracts. Therefore, the fact that the pellicles were washed before extracting by the "usual method" did not seem to have weakened the extract, when compared with extracts of unwashed pellicles. Furthermore, defatting the pellicles by method 7 did not result in a better extract. On the other hand, method 8, which was culture broth, appeared to be more reactive than any of the pellicle extracts, both by intradermal testing in dilution of 1:1,000, or greater, and by the scratch method. Similar differences were suggested from the tests with *Aspergillus niger*, although, as would be expected, the incidence of positive reactions was distinctly less with all dilutions.

When the results of skin testing with large and small aggregate extracts (methods 9, 10, 11, and 12) were presented in Pittsburgh in January, 1945, it was shown that there was very little difference in the reactivity between the large and small fraction extracts. Dr. George Rockwell pointed out that an equilibrium had been reached between the bag contents and the dialysate, and that Donnan's Law only had been fulfilled. This was obvious, though overlooked, since the cellophane bag had merely been changed and replaced in the original dialysate until a period of forty-eight hours had elapsed.

After the Pittsburgh meeting, methods 9, 10, 11, and 12 were repeated with *Alternaria tenuis* with the following modification: The bag contents were dialyzed against an equal volume of distilled water and the dialysate was removed for evaporation once every twenty-four hours, a quantity of distilled water equal to the measured bag contents being replaced for purpose of further dialyzation. It was found that after five days, or five changes of dialysate, practically no residue was left when the dialysate was evaporated to dryness in the drier. It was believed that all of the small aggregate had passed through the membrane. The five dried, gummy dialysates were added together, dissolved in Hollister-Stier solution in 1:20 ratio, and sterilized by Seitz filtration. The bag contents were

TABLE II

METHOD	ALTERNARIA TENUIS BC 17				
	Intradermal Tests				Scratch
	1:100,000	1:10,000	1:1,000	1:100	1:20
	Cases tested Reactions	Cases tested Reactions	Cases tested Reactions	Cases tested Reactions	Cases tested Reactions
No. 9-B Unwashed pellicle Small aggregate (dialysate)	20 0	19 3 16%	29 5 17%	16 5 31%	10 0
No. 10-B Unwashed pellicle Large aggregate (bag contents)	30 17 57%	29 20 69%	37 26 70%	25 24 96%	10 2 20%
No. 11-B Broth Small aggregate (dialysate)	30 4 13%	31 1 3%	39 9 23%	26 10 38%	10 4 40%
No. 12-B Broth Large aggregate (bag contents)	30 18 60%	31 23 74%	38 26 68%	25 24 96%	10 3 30%

Members performing studies from which above data taken:

Dr. Wm. L. Marr  
Dr. Ethan Allan Brown  
Dr. L. Dell Henry  
Dr. Erle D. Sellers  
Dr. J. H. Black  
Dr. Homer E. Prince

dried and extracted similarly. These extracts were denoted by numbers 9B, 10B, 11B, and 12B to distinguish them from those prepared in 1944. With certain other experimental extracts, they were distributed for skin testing late in 1945.

Although *Alternaria*-sensitive patients were available for experimental testing, the selection of persons clinically sensitive to *Aspergillus niger* was somewhat difficult. Therefore, in extract 9B and in all subsequent experimental extracts *Alternaria tenuis* only has been used.

Table II shows the results of skin testing with these extracts on *Alternaria*-sensitive patients. Although dialysis did not seem to separate *Alternaria* pellicle extract and *Alternaria* culture broth completely into skin-reactive and nonreactive fractions, a very definite tendency to retain skin-reactive fractions within the cellophane bag was observed. This failure to remove an aggregate of high skin reactivity from the bag contents was surprising. No explanation has been offered, unless it is on a basis of some peculiarity in the structure of the skin-reacting fraction of *Alternaria* extract. It has been suggested that the enzyme activity of *Alternaria* preparations may alter the permeability of cellophane sufficiently to interfere with dialysis.<sup>7</sup>

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# MOLD FUNGI IN THE ETIOLOGY OF RESPIRATORY ALLERGIC DISEASES

## VI. Intrinsic Fungous Factors in Relation to Asthma

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THE use of the term "intrinsic" in the title of this paper in reality is not correct. Actually, I wish to emphasize the thought that a patient may be sensitized to fungi which have become an integral component of the bronchial flora and thus he is exposed to more or less constant contact with an allergen.

Over a period of years we have studied the sputum of patients with asthma, both microscopically and by culture. In a small percentage of patients, there has been found what appears to be an infestation of the bronchial secretions by nonpathogenic fungi of various kinds. Extracts of these fungi have given excellent positive scratch and intradermal reactions in some patients. Passive transfer has been obtained. Improvement in symptoms has followed hyposensitization.

By this means, a small but significant number of patients have been definitely benefited. A few such patients presented no other sensitizations or other factors to explain their asthma and for them results have been striking.

That, briefly, is the thesis of this paper and it is my opinion that it is worth while to consider such a possibility in patients who either fail to respond to more routine measures or in whose sputum fungi are exhibited on initial routine examination.

### METHOD OF EXAMINATION

In our laboratory, routine study of the sputum consists of examining the usual stained smears for the character of the cells, the character of the usual flora, and tubercle bacillus. In addition, a fresh wet mount is examined by bright light for fungi and by darkfield for spiral organisms. Sometimes it is necessary to examine several specimens before representative findings are observed. If for any reason we suspect the presence of fungi, a spot plate is made on Sabaurand's or wort agar. This is done by selecting about 30 loopfuls of material and depositing them on the agar surface without streaking. The plates are sealed and incubated at room temperature for one to three weeks. If fungi which are cultivable by this method are present, colonies will develop from a varying number of the spot cultures. From such a culture one can get a fair gage of the intensity of the fungus infestation. Only rarely will all the spots develop colonies of fungi. The average specimen of significance

Presented before the Association of Allergists for Mycological Investigations, San Francisco, California, June 28, 1946.

will show positive spots in 25 per cent to 50 per cent of all spots cultured.

The patients, from whom such cultures are obtained, are subjected to careful examination to determine if the isolated organism is producing a mycosis *per se*. X-rays, blood studies, physical examination, et cetera, are made.

#### METHOD OF EXTRACTION

In each instance that positive fungus cultures are obtained, transfers are made into a broth culture of sufficient sugar concentration and correct pH to obtain heavy growth. As a rule, a dense mat of growth covers the surface of the medium within several days at room temperature. This is dislodged and pushed to the bottom of the flask and incubation continued. In a period of several weeks, four or five such mats are obtained in this manner in the same flask.

After sufficient growth is obtained, the flask is inverted and drained, the medium being carefully saved and filtered through a Seitz filter. To the remaining mats of fungus is added a sufficient amount of Coca's buffered saline to just cover the growth, usually 50 to 75 c.c. This mixture is allowed to extract for two days in the ice box and then filtered through a Seitz pad. A volume of glycerine equal to the filtrate volume is added and the finished product bottled. A few such extracts have been dialyzed and some have been concentrated by evaporation through a cellophane bag suspended in air. The latter have been used for experimental purposes. A bottle of the medium alone is kept on the testing tray to use as a control in skin testing.

I am well aware that such a crude method of extracting is open to certain theoretic objections. The main advantage is that the material examined has escaped the modifying influence of washing, drying, and chemical action which, I believe, modifies its properties to the extent that some of its antigenicity is destroyed. I admit the lack of experimental evidence to support this belief. However, comparative skin testing, using extracts prepared in various ways, convinces me that such a crude extract more often produces typical wheals by the scratch technique than do extracts prepared by more complicated and antigen-destroying methods. Also and without elaborate statistical analysis, I believe that false positive reactions are obtained in no greater frequency than with the most acceptable extracts of other types of material. Only rarely is a positive reaction obtained to the medium control.

No attempt has been made to identify properly all of the strains isolated. The majority have fallen into the aspergillus, the penicillium, and monilia-like groups. Also, we have found it difficult to maintain stock cultures without eventually obtaining growths which appear to be widely divergent from the initial growth. And we have not been able to make studies to determine any antigenic differences that might accompany morphologic or cultural variations such as we know exist among bacteria.

## CLINICAL RESULTS

The patients under consideration are the ones in whom no evidence of infection can be found. We conclude that in these patients the organism probably is nonpathogenic, is present in the respiratory tract, and is not invading the tissues or producing any reaction in the host other than possibly an allergic one such as would occur if pollens of other allergens were inhaled.

The patients, in whom there is no evidence of fungus disease but from whom positive cultures are obtained, fall into two groups. In one group, repeated cultures over a period of several months will show alternating positive and negative findings. This is true even with the most careful selection of specimens and using multiple plates for each specimen. This, I think, probably represents repeated exposure by inhalation of spores from some extraneous source, which, in the course of several days, disappear from the respiratory tract by natural means.

From the other group positive cultures are obtained on each cultivation. We interpret this as a true propagation of the fungus in the bronchial secretions or constant exposure to the spores from extraneous sources.

We are not prepared to furnish a statistical analysis of the results obtained by this approach to the study of allergens in patients with asthma. We can certify that only in over a period of twelve years we have been able to relieve a significant number of otherwise refractory patients by the use of such studies and treatment.

For attempts at hyposensitization, the crude concentrated extracts are diluted in ten steps and the concentration used for the beginning dose is the one which just gives a positive intradermal test. The results with treatment in this manner are exactly the same as with pollen therapy. The usual local reactions are obtained, constitutional reactions of mild degree are obtained with the higher doses, and the usual proportion of patients are seen who cannot tolerate large doses without an accentuation of asthmatic symptoms.

I wish to apologize for presenting my ideas and opinions on this subject without the bulwark of experimental work and statistical evaluation to support them. I can plead only that the limitations of private practice impose a definite limit to the work that can be devoted to research. I think my observations have extended over a sufficient period (twelve years) to warrant consideration and I offer this short note in the hope that others may be able to support or deny them.

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*The co-ordinative principle of science consists in the adjustment of each scientist's activities to the results achieved by others*—REVÉNO.

# MOLD FUNGI IN THE ETIOLOGY OF RESPIRATORY ALLERGIC DISEASES

## VII. Further Survey Studies

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Austin, Texas

SEVERAL years ago in a review on molds in relation to asthma and vasomotor rhinitis (Morrow and Lowe, 1943<sup>1</sup>), we devoted one section to surveys of air-borne molds. We mentioned the different points of view which had prompted these investigations and cited twenty-five studies including the early work of some of us (Prince, Selle, and Morrow, 1934;<sup>3</sup> Prince and Morrow, 1937;<sup>4</sup> Prince and Morrow, 1939;<sup>5</sup> Prince, Morrow and Lowe, 1939;<sup>6</sup> and Morrow, Prince and Lowe, 1942<sup>2</sup>), who now are engaged in a study being made, in collaboration by The Association of Allergists for Mycological Investigations and The University of Texas.

In a paper in 1942 (Morrow, Prince and Lowe<sup>2</sup>), we were able to point out specifically the following:

1. Molds are distributed widely throughout the central and southwestern United States.
2. Certain mold groups occur as dominant forms.
3. Total counts tend to be more uniform throughout the year in the South, reaching a peak in the fall.
4. The total counts in the North rise from a winter low to a maximum in the summer and fall.
5. The high total counts in the North equal, or exceed, the ones in the South.
6. *Alternaria* and *Hormodendrum* are encountered more frequently and occur in higher numbers than any other molds.
7. With few exceptions, the high total counts observed at all stations and the low total counts in the North during the winter represent the variation of *Alternaria* and *Hormodendrum*. A seasonal rather than a regional trend of these dominant species is indicated.
8. A seasonal trend is suggested in the occurrence of *Fusarium*.
9. Although *Aspergillus*, *Penicillium*, and certain other species also are encountered frequently, the numbers are low and the occurrence is uniform throughout the year, neither seasonal nor regional trends being apparent.
10. *Pullularia* is striking in the fact that, when present, it occurs as a "shower" at different stations and is a major portion of the station total. Since it is observed during both winter and summer and in the North as

From the Department of Botany and Bacteriology, The University of Texas, in collaboration with The Association of Allergists for Mycological Investigations. Read at a meeting of The Association of Allergists for Mycological Investigations, San Francisco, California, June 28, 1946.

well as in the South, it would seem that the occurrence is local and not seasonal or regional.

At sixteen member stations (Dallas, Temple, Waco, Houston, Abilene, Fort Worth, San Antonio, and Galveston, in Texas, and Shreveport, Toledo, Nashville, Evanston, St. Louis, Milwaukee, Kansas City and Minneapolis) plates were exposed during the two years in which these earlier observations were made. Membership at that time included twenty-five members. Some of them, however, did not expose plates and others were represented by another member station in the same city. Since then, the membership has been extended to include some fifty members. Not all of these have exposed plates, and some have become inactive.

After three years, the charter members discontinued plate exposures, but special plates were submitted from time to time. Newer member stations include some for which we have fairly complete data (El Paso, Little Rock, Miami, Superior, Decatur, Charleston, West Virginia, Boston, Pittsburgh, Memphis, and Buffalo). Others have a more or less incomplete record as to the number of and consistency in plate exposures.

A tabulated summary (Table I) for all of the stations, indicating when plates were exposed, by the month and year, reveals some interesting facts. Among other things, it can be seen that the sixteen charter member stations of 1939 were fairly consistent during the initial two-year period and that some of them continued the survey for longer periods, whereas Portland, Oregon, entered the survey only in April, 1946.

The table shows that thirty-one stations have had exposed plates examined at the laboratory at The University of Texas. A monthly report is based on four plates examined, two each of two different exposure dates. It can be seen that more than 600 plates were examined in 1939, 1940, and 1941, each, some 400 in 1942, and a fewer number since then, a total of almost 3,000 plates. Also, it can be seen that plates examined for each station vary in number from 228 for Galveston to 8 for Portland.

A column is added at the right of the table to show the last culture isolation for each member station. This number corresponds to the number of cultures isolated for the respective stations. For example, over a three-year period, 300 cultures were isolated and studied from the Minneapolis station. When some of them were found to be identical to isolations recorded earlier and kept as stock cultures, they were discarded, thus reducing the number of stock cultures for each station from the total number of isolates made. More than 5,000 cultures have been isolated and studied, varying from 4 for Portland to 686 for Houston, and the numbers for the respective stations are a reflection, in large part, of the period of participation in the survey by each station.

For the qualitative mold picture, certain stations were selected.

For one of the newer stations, Buffalo, plates were examined from September, 1944, through September, 1945. Table II shows the mold incidence during this period. Numbers for the total molds and the different



### TABLE I. SUMMARY OF ALL STATIONS

[illegible]

## MOULD FUNGI: FURTHER SURVEY STUDIES—MORROW

[illegible]

Member stations submitting exposed plates by years and months. Totals for the year based on four plates examined each month marked (+). Cultures isolated and studied for each station appear in the column at the extreme right. Isolates for each station are recorded and stocked by number (W-1 through W-300 for Minneapolis).

TABLE II. BUFFALO, NEW YORK

FUNGI	Month Plates	1944												1945												1946																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																															
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TABLE III. MEMPHIS, TENNESSEE

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SEPTEMBER-OCTOBER, 1947



genera are recorded; no species are indicated in the tables. Of *Hormodendrum* and *Alternaria*, counts of two and five were observed in September when the total count was sixteen. In the summary column on the right, grand totals are indicated for the thirteen-month period, *Hormodendrum* and *Alternaria* being twelve and fifteen of the total count of seventy-eight. The order in which the eleven genera appear in the table is that in which the molds appeared on the plates, beginning with the first plate examined. Below the table, the genera are listed in the order of their relative appearance, based on the total number of different molds isolated during the observation period. The ones most frequently encountered were *Alternaria*, unidentified sterile pale species, *Hormodendrum*, *Penicillium*, *Torula*, *Pullularia*, unidentified sterile species, and *Aspergillus*, in the order named.

Seasonal aspects can be noted. They are discussed in detail in longer reports which are sent to members from time to time. It can be seen that seven of the eleven genera appeared in September, two others were added in October, and one each in December and January. Only *Botrytis*, *Nigrospora*, and *Paecilomyces* were limited to a single appearance each.

Memphis, participating a year, February, 1944, to February, 1945, is tabulated similar to Buffalo (Table III) and a comparison is interesting. The dominant molds include *Hormodendrum*, *Alternaria*, unidentified sterile pale species, *Penicillium*, *Aspergillus* and *Pullularia*, the last two being confined to the fall-winter period. No great difference between Buffalo and Memphis was noted in the number of totals and the different genera. There was a larger number of molds which occurred only occasionally throughout the year, including those confined to a single month, such as *Torula*, *Paecilomyces*, unidentified pycnidial species, *Trichoderma*, *Verticillium*, *Rhizopus*, *Mucor*, *Spondylocadium*, and an actinomycete. *Alternaria* counts were high in May and January, *Hormodendrum* in May, July, October, and January, and *Aspergillus* in the fall and winter only. Memphis might be expected to have a local problem in mold allergy during a given month when these occasional forms appear on the exposure plate.

Pittsburgh was studied for almost three years. Tabulated, the picture is striking (Table IV). Actually, no more species were encountered in three years for Pittsburgh than for Memphis in one year. Moreover, with the exception of several species occurring but once each in 1944, the qualitative picture is similar for 1943, 1944, and 1945.

What then are the mold possibilities, as one reads the table, when considering a patient with allergy caused by molds? The dominant molds include unidentified sterile pale species, *Alternaria*, *Hormodendrum*, *Pullularia*, *Penicillium*, *Aspergillus*, *Torula*, unidentified sterile dark species, and *Trichoderma*; yeasts and *Oospora* are possibilities, and the ones occurring in only one month each, unidentified bulbiferous and pycnidial species, *Monilia*, *Verticillium*, and *Spondylocadium*.

TABLE V. DECATUR, ILLINOIS

FUNGUS	Month Plates	1941												1942												1943												1944																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																		
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TABLE VI. GALVESTON, TEXAS.

FUNGI	Month Plates	1939												1940												1941												Total	Alternaria Hormodendrum Sterile sp. pale Fusarium	Phoma Stemphylium Mycogone Curvularia "Bodies" sp.																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																					
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TABLE VII. GALVESTON, TEXAS

[illegible]

The appearance of *Trichoderma* is always interesting for it may be an indicator of textile deterioration—moldy clothing, tenting, rope, uniforms of the armed forces, and even the seabag. *Chaetomium* is another of the textile-rotting fungi, but it is noted less frequently on an air-exposure plate.

Whereas the picture for Pittsburgh was more or less consistent over three years, that for Decatur shows a number of molds appearing for the first time from year to year. One might think that industrial Pittsburgh would have a more changing aerobiology than the more rural Decatur. The table for Decatur (Table V) is interesting to study. Decatur has a more nearly perfect exposure record than any of the member stations; not one month did plates fail to come to the laboratory. The dominant molds include the usual *Alternaria*, *Aspergillus*, *Penicillium*, *Hormodendrum*, an unidentified sterile pale species, and *Pullularia*; the somewhat less usual *Fusarium* and *Phoma*, with several appearances each of *Mycogone*, unidentified sterile dark, sclerotial, and pycnidial species, and *Curvularia*. Ten species were noted only once each, and fourteen undetermined species made the list higher for Decatur than for any of the stations studied since the sixteen charter stations were retired. *Phoma* might be a problem there; also, a local problem might accompany the succession of species making a single appearance each from time to time.

The Galveston station exposed plates for more than five years (Tables VI and VII). The picture is "spotted" for 1939 and 1940, but fairly complete for 1941, 1942, 1943, and 1944. The dominant molds include ten genera, with the appearance of fourteen to ninety-three over the five-year period, such as *Alternaria*, *Hormodendrum*, unidentified sterile pale species, *Penicillium*, *Aspergillus*, and *Pullularia*. By adding the totals and corresponding genera in the two tables, it can be seen that the order changes little in the early and later periods. Only six of thirty genera made a single monthly appearance, *Paecilomyces*, *Nigrospora*, *Cephalosporium*, *Stachybotrytis*, *Sporotrichum*, and *Verticillium*. There is an interesting point in connection with the place of dominance of *Alternaria*, with 93 appearances in the 574 total molds for Galveston. Some of us (Prince, Selle and Morrow) did not even list *Alternaria* with the molds reported in 1937 from Galveston.<sup>4</sup> From the later results, it can be seen that *Alternaria* is the one mold that was recovered each month of each year during the period of more than five years.

Again speculation is invited as to a possible problem at Galveston with the occasional molds which indicate seasonal groups in many instances, such as *Nigrospora*, *Trichoderma*, *Oospora*, and *Paecilomyces*, which appear only in the spring months.

Three points seem outstanding in these results which have been presented.

First, there is a "top ten" group of genera for all stations, which include the dominant ones in nearly every instance when they are shown for a station, whether studied for one year, two, or five:

*Alternaria*  
*Hormodendrum*  
*Penicillium*

*Aspergillus*  
*Pullularia*  
 Sterile pale species  
 Sterile dark species

*Torula*  
*Fusarium*  
*Trichoderma*

Secondly, in the ten dominant molds for all stations there is a "big six" for each station, which may or may not be seasonal. For the stations discussed in this report they can be listed as follows:

Buffalo  
*Alternaria*  
 Sterile pale species  
*Hormodendrum*  
*Penicillium*  
*Torula*  
*Pullularia*

Decatur  
*Alternaria*  
*Aspergillus*  
*Penicillium*  
*Hormodendrum*  
 Sterile pale species  
*Pullularia*

Memphis  
*Hormodendrum*  
*Alternaria*  
 Sterile pale species  
*Penicillium*  
*Aspergillus*  
*Pullularia*

Galveston  
*Alternaria*  
*Hormodendrum*  
 Sterile pale species  
*Penicillium*  
*Aspergillus*  
*Pullularia*

Pittsburgh  
 Pale sterile species  
*Alternaria*  
*Hormodendrum*  
*Pullularia*  
*Penicillium*  
*Aspergillus*

The third point concerns the occasional types. May they not be significant not only as a part of the total aerobiology picture for a particular station, but possibly as the factor in many stubborn clinical cases of inhalant respiratory allergy of which the cause does not fall into the better known mold groups? An analysis of surveys is heartening to the physician who does routine testing with the "top ten" or the "big six," but may he not be challenged also by *Trichoderma* that appears only in May or *Rhizopus* in October in his particular area? We cannot discount them, and we should remember that a single colony on a two-minute plate theoretically is equivalent to a pollen count of twenty-one (Prince and Morrow, 1937).<sup>4</sup>

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# MOLD FUNGI IN THE ETIOLOGY OF RESPIRATORY ALLERGIC DISEASES

## VIII. Mold Allergy in West Texas—Clinical Observations

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Abilene, Texas

A STUDY of incidence of molds in the Abilene, Texas, area has been conducted by us since 1938. A part of this study is included in the general survey made by the Association of Allergists for Mycological Investigation, under the supervision of Dr. Marie B. Morrow and her associates, of the University of Texas. Dr. Homer Prince, of Houston, Texas, especially deserves credit for initiating this work.

Dr. Morrow's tabulations, compiled from plate agar exposures obtained from various stations over the country, are recorded elsewhere. Her survey has been of great value to all of us interested in this field. From the beginning, however, we have felt that exposed slide counts also give valuable information. Such slide counts have been made daily in Abilene since 1938 and tabulated with daily pollen counts which were begun years earlier. The difference in the form and structure of the spores on the exposed slides makes accurate differentiation impossible, but the daily study of the slides gives a fairly reliable index of the general incidence of the molds.

*Alternaria* forms are identified readily and a tabulation of this group gives a helpful picture of the molds in general in this section where *Alternaria* is the most numerous of the dominant groups. *Alternaria* occurs throughout the year in Abilene. The counts are lower in the earlier months of the year and increase in May, with intermittent high counts well into December. According to Dr. Morrow's report, this seasonal incidence is more marked in the North and Middle West than in the South and Southwest.

This seasonal incidence of *Alternaria* and other molds is of definite clinical importance. In our section, pollinosis is perennial. The important offenders are mountain cedar, the ragweeds, the Chenopodiales group, the grasses, and certain trees, particularly mesquite and oak. The *Alternaria* counts consistently are higher than any of the pollen counts, except during brief periods in the fall and winter when the mountain cedar peaks are extremely high. The molds may cause inhalant allergic symptoms at any season and add to confusion in diagnosis during periods when both molds and pollens are high.

In this study we have reviewed the records of 392 new patients with inhalant allergy, encountered in private practice in a five-year period from 1941 through 1945. Inhalants used in testing included common pollens, familiar miscellaneous inhalants, and eight mold extracts. The mold ex-

Presented before the Association of Allergists for Mycological Investigations, San Francisco, California, June 28, 1946.

TABLE I. SYMPTOMATOLOGY  
(392 Cases Inhalant Allergy)

	Asthma		Hay Fever		As. & H.F.		Misc. Conditions	
	No.	%	No.	%	No.	%	No.	%
Molds only	13	3.3	10	2.2	6	1.5	4	1.0
Mixed molds	45	11.4	59	15.0	25	6.3	12	3.0
Total	58	14.7	69	17.6	31	7.8	16	4.0

TABLE II. AGE INCIDENCE  
(174 Cases Reacting to Molds)

	Total	1-20 Years		Over 20 Years	
		No.	%	No.	%
Cases Reacting to Molds Only	33	25	75.7	8	24.2
Cases Reacting to Molds and Other Inhalants	141	71	50.3	70	49.6

tracts were prepared by Dr. Prince from cultures which were isolated by Dr. Morrow from exposed plates submitted by various members of this Association. Extracts used were those of *Alternaria*, *Aspergillus*, *Curvularia*, *Fusarium*, *Helminthosporium*, *Hormodendrum*, *Spondylocadium*, and *Penicillium*. All testing was done by the intracutaneous technique. Only moderately or strongly positive reactions were tabulated in this study.

Of the 392 patients, 174, or 44.3 per cent, gave reactions to one or more mold extracts. Thirty-three of the patients, or 8.4 per cent, reacted only to molds. One hundred forty-one, or 35.9 per cent, gave reactions to molds and other inhalant extracts.

Of the 392 patients with inhalant allergy, fifty-eight, or 14.7 per cent, with asthma reacted to molds. Thirteen, or 3.3 per cent, of them reacted only to molds. Sixty-nine, or 17.6 per cent, with hay fever reacted to molds, with 10, or 2.2 per cent, reacting only to molds. An additional group of thirty-one patients, having both asthma and hay fever, added to these figures. Sixteen patients had symptoms of inhalant allergy other than asthma and hay fever, chiefly allergic rhinitis or allergic bronchitis (Table I).

The age of patients who manifest mold sensitivity is of particular interest to us. Of the 392 cases, ninety-six sensitive to molds were in the early age group, one to twenty years. Seventy-eight sensitive to molds were over twenty years of age. Of added interest was the fact that of thirty-three patients reacting only to molds twenty-five, or 75.7 per cent, were in the youngest age group (Table II). From general observation, especially in the last two years, we have been impressed even more with the importance of mold sensitivity in children. From January to June, 1946, the incidence showed a relatively high percentage of mold sensitivity in the younger age group.

Passive transfer studies were not made routinely in the clinical testing

of these patients. The method was used repeatedly, however, in experimental studies. We have never failed, on trial, to effect a passive transfer with a serum of a patient sensitive to mold extracts. We have used the method of exhaustion of passively transferred sites, in an attempt to determine whether or not a common atopen is present in extracts of the various mold species. Limitation of time and space prevents a detailed report of these experiments. We gained the impression, but an impression only, that there were common atopens in extracts of certain groups. On the contrary, extracts of the dominant *Alternaria* group consistently did not desensitize sites sensitized to *Curvularia*, *Spondylocladium*, or *Hormodendrum*.

#### TREATMENT

This is only a brief summary of results from treatment. We have tried to tabulate these results from an objective standpoint and only from a perusal of the records. Of the thirty-three patients sensitive only to molds, twenty-one, or 63.6 per cent, gained complete or marked relief from symptoms. Of the 141 patients sensitive to molds and other inhalants, seventy, or 49.4 per cent, obtained satisfactory results from treatment.

We feel that these results, although not striking, are distinctly worth while. Results of treatment in the pure mold-sensitive group compare favorably with results in the pure pollen-sensitive group.

#### SUMMARY

1. A study of exposed slides over a period of five years has shown that molds are present throughout the year in the Abilene, Texas, area. A study of exposed agar plates have corroborated this observation. Proper identification of the various molds can be made only after isolation from agar plates. Both methods are of value. *Alternaria* forms are readily identified by the slide counts, and they and other identified forms should be included in pollen counts.

2. Of 392 new patients with inhalant allergy, studied over a five year period, 1941 to 1945, 174, or 44.3 per cent, gave definite reactions to one, or more, of the mold extracts. Thirty-three cases, or 8.4 per cent, gave reactions only to molds.

3. In the younger age group, one to twenty, mold sensitivity particularly is prevalent.

4. Therapy by desensitization is worth while.

The authors wish to thank Miss Nell Glass and Miss Inez Darden for technical assistance in these studies.

## THE INCIDENCE OF IDIOBLAPTIC CIGARETTE SENSITIVITY

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THE choice of the title of this communication may strike some as odd and indeed too wanting in exactness from the point of view of the specificity of allergic sensitivity to be scientifically acceptable. Nevertheless, this study of the frequency of idioblaptic sensitivity to cigarettes among subjects of that category of allergic disease may be justified because of the greatly preponderant preference of smokers for tobacco in that form. Moreover, for a number of reasons, it would be impracticable to attempt such a study as this with the separate components of the commercial cigarettes.

The published reports with which the present one can best be compared or contrasted are the well-known ones of Harkavy and of Sulzberger. Both of these investigators examined subjects with respect to the possible presence of cutaneous sensitivity to tobacco, employing extracts of pure tobacco in the familiar intracutaneous tests, and both reported an unusually high percentage of positive reactions following direct tests in subjects with thromboangiitis obliterans.

In three series of such patients, Harkavy and his associates found 83, 86 and 87 per cent of positive reactors. Sulzberger and Feit in a smaller series of twenty-four cases of (thromboangiitis obliterans) found 78 per cent positive.

It is noteworthy that Harkavy<sup>4</sup> found in a control series of smokers 20 per cent and in non-smokers 12 per cent of positive reactors. Of obvious significance is the report of Sulzberger and Feit<sup>5</sup> that passive transfer of the cutaneous sensitivity (Prausnitz) failed in twenty-one of the twenty-two patients with thromboangiitis obliterans, nineteen of whom showed positive intracutaneous reactions in the direct tests. The one patient whose serum contained passively transferable anti-tobacco reagin was, in like manner, found to be reaginically more sensitive to house-dust than to tobacco. This result is reasonably comparable with that reported by Aaron Brown<sup>1</sup> among his asthmatic patients—about 1 per cent were reaginically sensitive to tobacco.

Sulzberger and Feit<sup>5</sup> write:

"Our findings of the general lack of reagins, in spite of immediate wheal reactions to tobacco in thromboangiitis obliterans, is in contradiction to the results of Harkavy et al<sup>†</sup>. These observers report that the wheal hypersensitivity to tobacco is associated with the presence of 'atopic reagins' to tobacco in thromboangiitis obliterans; and that they were able to demonstrate such reagins in thirteen out of twenty tobacco-positive cases of thromboangiitis obliterans. And that: 'The presence of reagins to tobacco in these thromboangiitis cases indicates that we are dealing

<sup>†</sup>Harkavy, Hebal and Silbert: *Proc. Soc. Exper. Biol. & Med.*, 30:104-107, 1932

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with individuals who were in all probability atopic, and that the positive phenomena are true antigen-antibody reactions.'"

Sulzberger and Feit<sup>5</sup> remark further:

*"However, our above reported results must classify thromboangiitis obliterans as a condition usually associated with a specific and marked hypersensitivity of the vascular apparatus of the skin to tobacco, but without any at present demonstrable connection with asthma, hay fever, and disseminated neurodermite, et cetera, and, in our cases, without regularly demonstrable reagins."* (authors' italics)

Some years ago, I had some part in arranging for an investigation of this question in a hospital service specializing in the study and management of thromboangiitis obliterans. The tests were carried out by an experienced investigator, Katherine L. Bowman, with ample clinical material and controls and with the skillful use of the Prausnitz experiment. The results confirmed those of Sulzberger and Feit in the clearly demonstrated absence of reaginic sensitivity to tobacco to any noticeable extent more in the thromboangiitis obliterans group than in the control group.

Miss Bowman summarized her hitherto unpublished findings as follows:

"1. Comparing the results obtained by testing sixty-nine thromboangiitis obliterans patients and sixty normal smokers with tobacco and other allergens, it was found that there is practically no difference in the percentage of positive reactions to tobacco in the two groups, if one-plus and plus-minus reactions be disregarded.

"2. If the one-plus and plus-minus reactions be included, the difference between the percentage of positive reactions to tobacco obtained in the thromboangiitis obliterans group and that obtained in the normal group is not of sufficient magnitude to be significant.

"3. The skin response to histamine 1:1000 was found to be slightly greater in the thromboangiitis group than in the normal group.

"4. The incidence of positive reactions to ragweed pollen, timothy pollen, and horse dander, was found to be equal in both groups, showing the same distribution of allergy in the two series.

"5. With one exception, passive transfer of the tobacco reactions in the thromboangiitis obliterans group was successful only when a positive passive transfer was obtained with one or more of the other allergens tested.

"6. The incidence of positive tobacco reactions was found to be even higher in a group of twenty-three normal nurses than in the group of sixty normal men.

### Conclusions

"1. There is no evidence in this study to indicate that there is a higher incidence of *specific* cutaneous sensitivity to tobacco in thromboangiitis patients than in normal men.

"2. Any slight excess in the number of one-plus reactions to tobacco which may have been found among the thromboangiitis obliterans cases might possibly be due to the same factor which is responsible for the increase in the response by this group to the nonspecific excitant, histamine 1:1000."

It is seen that Miss Bowman agrees with Sulzberger and Feit in denying the existence of a reaginic (transferable) sensitivity to tobacco as characteristic of thromboangiitis obliterans. However, her findings do not



support the conclusion of those investigators that thromboangiitis obliterans is "usually associated with a specific and marked hypersensitivity of the vascular apparatus of the skin to tobacco without regularly demonstrable reagins."

In the extended study in the past ten years of over one hundred patients affected with idioblastic allergy, I have encountered a number of instances of nonreaginic sensitivity to cigarette-smoke as recognized by symptoms and accompanying specific tachycardia. In the greater part of this period, I tested only the habitual smokers in this respect, overlooking the possibility that exposure to the smoke of others can suffice to cause allergic symptoms, and forgetting that the constitutional nonreaginic sensitivity to an allergen is frequently established long before the subject has arrived at the age of *symptomatic* reactivity.

Soon after the first instances of symptomatic cigarette sensitivity were identified, all new patients were requested not to smoke while the early exploratory tests were being carried out; and I was astonished to find that in a few instances cigarette smoke was the sole pulse-accelerating allergen and that all symptoms disappeared shortly after smoking was discontinued.

*Case 1.*—In J. B., a chemist, the allergic symptoms, that is, those which disappeared in the period in which the subject reduced his smoking to a mere evening test (one cigarette), were *abnormal tiredness*, "nervous indigestion," severe headaches, neuralgia, et cetera. The daily pulse range in the period (barring the test) was 68 to 78. The highest count while smoking was 92.

*Case 2.*—In Mrs. S., aged twenty-eight, the allergic symptoms (meaning in this case also those that disappeared permanently after she discontinued smoking) were "deadly tiredness," nervousness, fearfulness, constant "chest colds," painful, crampy menstruation and constipation. After avoidance of smoking, the pulse range of this patient was 70 to 76. The highest count while smoking was 100.

Three patients have been observed in whom petit mal (two) or grand mal (one) seizures have been induced by cigarette smoke or smoking.

In the first of these, a petit mal reaction followed within a few minutes after the patient (M. S., eleven years old) began breathing through the folds of a handkerchief into which cigarette smoke had just been breathed.

In the second epileptic patient (M. A., eighteen years old) a lumbar sympathectomy (Danzis) had left only a small list of dietary allergens, chiefly egg. Over a period of three months thereafter, she was in daily technical service without seizures. On two occasions in that period while she was avoiding all food allergens, she was heavily exposed at her apartment to cigarette and cigar smoke. Each time she suffered a seizure, once without convulsion and once with typical grand mal convulsions. On both occasions the seizure occurred very soon, within about a half hour, after the exposure to the smoke.

The third epileptic patient (J. K., aged thirty) who had been avoiding his ten pulse-accelerating food categories and tobacco for eight months and had been free from seizures during that time, deliberately induced a grand mal seizure by smoking cigarettes. The smoking began on a Friday evening. On waking Saturday morning, the subject experienced sensations that he recognized as those customarily

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presaging a seizure. He resumed smoking and in the late morning fell in a major convulsive seizure in which he was attended by a nearby physician, who recognized the condition as epileptic and prescribed dilantin. The patient disregarded the prescription. He has not smoked in the succeeding five years and has observed his rather stringent dietary restrictions. In that period there have been no seizures.

In the past few years, I have had more frequent occasion to test allergic persons for nonreaginic sensitivity to cigarette smoke, and had acquired an impression that this particular sensitivity is perhaps more common than any other. My special examination of this question has amply confirmed that impression, although the number of suitable persons at disposal for the study is not sufficient to permit anything more than an approximate estimate of the percentage incidence of cigarette sensitivity among the population.

The reference to "suitable persons" calls for explanation. The satisfactory identification of an allergen through the criterion of specific tachycardia can usually be made only if the individual's normal pulse range is known and if he is not, at the time of the test, under some food-allergic influence. For example, L. B., whose pulse rose from 60 to 69 while smoking was not on that account allergic to cigarettes because her normal range is known to be 58 to 70; but the rise in Dr. J. from 60 to 72 indicated sensitivity in this patient since his normal range is 58 to 62. On the other hand, if the test is made several hours after a meal when the pulse is steady, a rapid rise of 16 beats or more, especially if the highest count is 88 or higher, clearly indicates specific sensitivity to cigarette smoke, even if the subject's pulse character has not been determined.

Before taking up the statistical survey of cigarette sensitivity, it is necessary to discuss a certain interpretative complication.

Tobacco occupies a special position among allergens by reason of the high primary toxicity of its characteristic chief alkaloid nicotine. Hence, the question arises how shall one distinguish the toxic symptoms of tobacco from the allergic; and since this question applies, in the present discussion, only to man it would seem to be a reasonable requirement that the study of the primary toxic effect of tobacco be made in persons known to be free from familial allergy. However, since only about 10 per cent of the population can qualify in that respect, it may be considered probable that most of the human subjects who have served as experimental material in such studies were allergic, and it is conceivable that they *may* have been *selected* because of their susceptibility to tobacco, which was not recognized as allergic.

The symptoms of "tobacco-poisoning" such as commonly occur in smoking, are just those that are sometimes observed in persons who are extremely allergic to nontoxic foods—"burning in the mouth, a scratching sensation of the pharynx, increased salivation (later dryness in the mouth), headache, vertigo, confusion, disturbed vision and hearing, nausea,

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TABLE I. PULSE RECORDS OF SMOKING TESTS IN  
CIGARETTE-SENSITIVE PERSONS

Subject	Sex	Normal Pulse Range	Rate Before Smoking	Rate at Intervals After Starting Smoking Time in Minutes							
				3'	6'	9'	12'	15'	30'	Other	
M. S.	F	64-74	72, 72	76	76	76	78	78(S)	74		
M. M. D.	F	70-80	78	88	88(S)	84	84	84			
L. P.	F	60-72	64	80	76(S)	80	74	72			
A. W.	F	66-78	73		74	87(S)		84	80		
W. S. C.	M	46-62	62	94	90(S)	90	88	85			
J. B.	M	68-78	78		92(S)						
A. R.	M	70-84	76, 76	80	84(S)			90	90		
A. K.	M	68-76	72	86	82	82	82	82(S)			
E. A. C.	M	69-81	85, 85		119	108(S)			40' 82		
B. S.	M	68-84	82, 84	Cold empty tobacco pipe in mouth			104(S)		40' 90		
J. C.	M	49-64	57, 64				30' 74	60' 76	90' 74(S)		
Dr. J.	M	58-62	60					72	70	60' 68(S)	
E. C. R.	F	69	79	4' 90(S)				79			
Mrs. S.	F	70-76	72		5' 100(S)			92	90		
F. M.	F	66-74	66	stopped smoking } 15'		20' 82	30' 76	60' 70			
M. A.	F	58-73	71		5' 92(S)						
M. O. N.	F	Min. =64	80	2' 92	5' 98(S)				80		
G. M.	M	66-76	74	1' 80	3' 78	6' 78	9' 80(S)	12' 72	15' 72		
M. M.	F	60-72	72	1' 90	3' 92(S)	6' 86	9' 86	12' 78	15' 80	18' 76	21' 74  24' 72

S = Stopped smoking

Not included in this list are two persons known to be clinically sensitive to cigarette smoke in whom the smoking test was not done.

D. Clark's case and the case of J. K. (epileptic) are also not included.

vomiting and diarrhea. Pulse at first increased, then irregular. Subsequent depression.”\*

Three of these symptoms may also be toxic, namely, nausea, vomiting,

\*Slightly altered from Torald Sollmann's *Manual of Pharmacology*, fifth edition, p. 393, describing the effects of poisoning with pure nicotine on man.

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TABLE II. PULSE RECORDS OF SMOKING TESTS IN  
CIGARETTE-INSENSITIVE PERSONS

	Sex	Normal Pulse Range	Rate Before Smoking	Rate at Intervals After Starting Smoking Time in Minutes					
				3'	6'	9'	12'	15'	30'
C. W. C.	M	61-69	(1) 64 (2) 61	65 61	66 68	66 66	66 64	62 (S) 62 (S)	
L. B.	F	58-70	70, 60	60	69	66	65 (S)	65	
S. I. H.	M	68-80	72	72	72	72	72	72 (S)	
Dr. W.	M		74		74	74		76	74 (S)
D. F.	M	58-68	72	72	72	72	68	68 (S)	
R. S.	F	42-56 (?)	47, 45	45	44	43	43	43 (S)	
W. S. C. Jr.	M		66	66	67 (S)	67	65	68	
M. C.	F		62	60	56	56	58	62 (S)	
D. J.	M	70-76	72, 74	76	76	76	76	76 (S)	
R. La T.	M		68	68	68	68	68	68 (S)	
H. H.	F	60-66	(1) 66 (2) 64	66	Smoking one hour (64-66)			64	66 (S)
Dr. S.	F	66-76	74	74	66	66	70	74 (S)	inhaled
F. S.	M	72-84	84	84	84	84	84	84 (S)	
Mrs. J.	F	68-76	(1) 76 (2) 76	76 76	76 76	78 (S) 76 (S)			
Dr. R.	M	70-76	76, 72	30' 74	60' 74	90' 72	continuous smoking		
M. P.	F	59-72	60, 59	3' 59	6' 60	9' 59		14' 60 (S)	25' 62
E. B.	F	72-76	82	3' 82				60' 82	20' 82 (S)
R. K. P.	M	51-61	56		5' 57	15' 57	30' 55	45' 57	75' 54 (S)
A. S.	F	70-76	70	3' 66	10' 66	15' 68	24' 70	35' 70 (S)	

S=Stopped smoking.

and diarrhea, since they are observed in presumably nonallergic lower animals.

The observations described in the present writing make it seem rather likely that the symptoms observed following smoking in some persons are usually allergic rather than toxic. Certainly no pharmacologist would attempt to explain on a nonspecific, toxic basis the occurrence of epileptic seizures in one person, constipation without headache in another, and in still another, severe headaches without constipation, all proved to have been caused by smoking.

Against an explanation of these symptoms on a toxic basis speaks also the fact that in about half of the individuals *tested* and reported in this article the pulse-rate was not perceptibly affected by smoking and that

symptoms were experienced by only a small fraction of the entire group studied.

In animals toxic doses of nicotine do not exhibit such great variation.

The foregoing considerations, together with the demonstrated significance of allergic tachycardia, justify the separation of the two groups of persons in the tables.

In Tables I and II are listed, respectively, cigarette-sensitive and cigarette-insensitive persons, all individuals of both groups having been identified as subjects of idioblastic allergy. It is noteworthy that in both groups the two sexes are about equally represented. Nearly all of the subjects had been relieved of their allergic symptoms through the pulse-controlled dietary analysis. Hence, the tests of the effect of cigarette smoking were in each instance carried out by persons having a long experience of numerous daily pulse-counts and a dependably exact acquaintance with the normal and the abnormal variations of their pulse rate.

This consideration alone justifies the interpretation of the pulse-record of G.M. as indicating a specific allergic reaction to the cigarette smoke, although the maximal rate was only 4 beats above his normal maximum. However, this subject had been for some time aware of a distinct clinical sensitivity to tobacco smoke (nausea, acute conjunctivitis).

In my monograph<sup>3</sup>, on pages 86 and 87, I have discussed briefly the question whether the significant allergic excitant of tobacco may be nicotine. This question seems a reasonable one because of the known instances of severe allergic symptoms caused by other alkaloids (quinine, morphine). I mentioned also the case of a colleague who experienced unpleasant symptoms when smoking ordinary tobacco but not when smoking "denicotinized" (Sano) tobacco. I am indebted to that colleague, Dr. Guy W. Clark, for the following history of his case and the record of his pulse-counts in the several tests of ordinary and Sano tobacco.

The patient, a man aged fifty-nine, has never had hives or heartburn. He has had evidence of indigestion manifested by gas formation and the frequent appearance of canker sores, but he has had no "nervous sensation," neuralgia, hayfever, asthma or any other signs of food allergies except occasional dizziness when smoking ordinary tobacco. Patient inclined to be underweight but very active in outdoor occupation. He has been an off-and-on smoker from age twenty to forty. For the last twenty years has smoked quite regularly but never to excess, twelve to fourteen cigarettes per day maximum.

In 1939 he experienced an angina-like pain and was examined by a well-known cardiologist who found no organic defects. From the patient's description of his troubles (tachycardia, frequent pain in the left side and excessive gas formation), the physician advised him to stop smoking for a while and see if any benefits were noticed. Being a pharmacologist and quite familiar with drug action, the patient, feeling that the moderate smoking could not be the cause of the trouble, declined to follow the advice of the physician and continued smoking.

In 1942 because of excessive gas formation, the patient consulted an eminent gastroenterologist in Chicago, and after a complete examination, including x-ray of the entire intestinal tract, the advice again was to stop smoking. While discussing the

situation with another physician in New York City, it was suggested that "denicotinized" cigarettes be substituted for the regular brand which had been used. The patient has now used "denicotinized" tobacco mostly as cigarettes but also in pipe-tobacco for more than three years and has been entirely free from the cardiac symptoms and practically free from any signs of indigestion.

While recovering from an eye operation last spring, the patient decided to stop all smoking; this as on previous similar occasions, was followed by some improvement in appetite. This patient has always had low blood pressure, 110 to 120 systolic, and a customarily slow pulse rate, 60 to 66.

### *Experiment*

#### *Pulse Rate*

Dec. 16—6:00 P.M.—60 (before dinner)  
                                 62  
                   6:25 P.M.—68 (right after first puff of "denicotinized" cigarette)  
                   6:30 P.M.—78  
                   6:35 P.M.—80 (end of cigarette)  
                   8:45 P.M.—62  
                                 64  
 Dec. 18—2:40 P.M.—68 (soon after using tuamine inhaler)  
                                 70  
                   2:44 P.M.—70 (repeated tuamine, both nostrils)  
                   2:45 P.M.—74  
                   2:46 P.M.—76  
                   3:05 P.M.—66  
                   3:08 P.M.—66 (lighted standard brand of cigarette, long)  
                   3:10 P.M.—86  
                   3:15 P.M.—90  
                   3:20 P.M.—84 (end of cigarette)  
                   6:00 P.M.—60 (before dinner)  
                                 62  
                   6:45 P.M.—64 (right after dinner)  
                   7:00 P.M.—68  
                   7:25 P.M.—64  
                   7:30 P.M. (lighted "denicotinized" cigarette)  
                   7:32 P.M.—74  
                   7:35 P.M.—74  
                   7:37 P.M.—76 (end of cigarette)  
                   7:40 P.M.—78

Dr. Clark's experiment, as he says, does not prove the allergic excitant to be nicotine; it does not even indicate that there is not more than one allergen in the usual smoking forms of tobacco. However, it leaves no doubt that the partly denicotinized tobacco is, whether for a qualitative or a quantitative difference, distinctly less allergenic than ordinary tobacco.

It is, of course, conceivable that subjects more allergic to the cigarette allergen would not experience the differences between the two products that are reported by Dr. Clark. With the expression "more allergic" I am referring to shock-organs, particularly the renal, that may be affected by lesser concentrations of the tobacco allergen and which are not involved in Dr. Clark's case.

### SUMMARY

1. Reaginic sensitivity to tobacco affects only a small percentage of the population (about 1 per cent according to Aaron Brown). Symp-

toms proved to be due to reaginic sensitivity to tobacco have not been reported.

2. A number of instances of idioblastic (nonreaginic) sensitivity to cigarette smoke are described in whom different characteristic symptoms were experienced (epileptic seizures, dizziness, headache, constipation, abnormal tiredness, indigestion, "fearfulness," menorrhagia). In all cases the symptoms ceased when smoking was discontinued.

3. With the criterion of specific tachycardia, it has been found that about half of all nonreaginic food-allergic persons of both sexes are allergically sensitive to cigarette smoke.

4. In one case the smoking of partly denicotinized tobacco caused an elimination of the symptoms (dizziness) and a distinct reduction of the tachycardia (two tests) that regularly followed smoking of ordinary tobacco.

#### ADDENDUM

After I had dispatched the manuscript of this paper, I received a letter from Dr. Clarence W. Lieb, calling my attention to the similar study of Harry L. Segal,<sup>‡</sup> in which much of my findings were anticipated, though differently interpreted.

In this study of six patients, whose chief complaint was fatigue (one of the most frequent allergic symptoms), a constant finding was marked acceleration of the heartrate, (up to 100 or more in all). The fatigue was "relieved" in all of these persons after cessation of smoking.

Segal is careful to report that "not all patients who are tired and who smoke are improved by discontinuing the smoking." Thus he noticed the limitation of the described relationship to *certain* individuals, yet this specificity did not suggest allergy to him, and after excluding other irritants from consideration, he ascribed the effects to the pharmacologic action of nicotine, which he found effective in some persons in relatively small "dosage."

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#### INSUFFLATION OF SULFONAMIDE DRUGS

(Continued from Page 433)

the cough would continue to develop in many patients but not in as many as had been formerly observed. The numbers in whom sinusitis and the various forms of otitis developed were definitely lessened when compared with the numbers of patients not so treated in whom these complications appeared. The greatest value of the insufflation of the powdered sulfonamide compounds appeared to be in the first three or four days of the acute infection. Insufflation of the sulfonamide compounds proved to be as safe as their oral use. Only seven out of the 1,500 treated gave evidence of sensitivity as manifested by dermatitis, hives or hay fever-like symptoms.

# THE USE OF SEX HORMONES IN ALLERGIC DISORDERS

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WHILE obtaining the initial history of a female patient with an allergic disorder, the physician may unearth a tendency to exacerbation or onset of symptoms during the premenstrual phase or during actual menstruation. After the proper elimination and desensitization measures are instituted, such a tendency may still be apparent, although to a lesser degree. Patients who previously were ill throughout the entire cycle may now be consistently affected only during one phase of it. Several months of observation while under standard allergic management may be necessary to establish these facts. Keeping combined menstrual and symptom calendars is a worth-while procedure, for without such a permanent record valuable information may be overlooked.

The adolescent girl may lose or may start clinical manifestations of allergy at puberty; exacerbation of previous difficulties at this time is common. Quite frequently women whose allergic disorders have been well controlled may have marked exacerbations at the climacteric. Both the loss and the acquisition of allergic disorders are commonly noted at the menopause.

Pregnancy may exert either a beneficial or an adverse effect on the course of allergy. Indeed, it is the author's experience that it is more likely to follow one of these courses than to leave the allergic state unaffected. Pregnancy gives rise to disorders peculiar only to the gravid state; in latter years there has even been a suspicion that the early toxemias of pregnancy may be due to an endogenous hormone allergy.<sup>6,7,29</sup>

All of these repeatedly observed phenomena obviously must have some relation to ovarian and anterior-pituitary gland function. Study of the normal pattern of female pituitary and sex hormone physiology and of the deviations found in the cases under discussion yields information not only interesting but therapeutically useful. Rational hormone therapy to aid specific allergy management is the welcome result.

## ENDOCRINE DYSFUNCTION AND ALLERGIC MANIFESTATIONS

That specific sensitivities, important as it is to know them, are not the only factors concerned in the production of allergic manifestations is well known. Why a given allergen can at one time provoke a clinical manifestation of allergy and at other times not is determined by other factors which modify the allergic balance. Dysfunction of the autonomic nervous system, infections, the emotional state, and endocrine dysfunctions are among the most important factors.

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Presented at the second annual meeting of the American College of Allergists, San Francisco, June 30, 1946.



Endocrine dysfunction may bring about clinical manifestations of allergy in any one or more of the following ways:

(a) By affecting the balance of the autonomic nervous system toward a parasympathetic preponderance.

(b) By affecting the emotional state of the individual so that he is more labile psychosomatically.

(c) By lowering his resistance to infections, which usually cause exacerbations of clinical allergy.

(d) By disturbing the allergic balance through excess or deficiency of specific hormones, or through hormonal imbalance.

(e) By primary allergy to endogenous endocrine products.<sup>38</sup>

(f) By the possibility of anti-hormones to gonadotropins administered therapeutically causing secondary reactions.<sup>34</sup>

#### RECOMMENDED METHODS FOR QUANTITATIVE HORMONE STUDIES

It is obvious that quantitative measurements of the various ovarian and pituitary hormones in the blood or urine are necessary for the diagnosis of obscure cases and advisable in the seemingly obvious ones. Unfortunately, all of the tests are characterized by being rather complex and time-consuming. Out of the large number available, the author prefers the following four:

- (1) Fluhmann's test for thyliakentrin in blood;<sup>8,9,11</sup>
- (2) The vaginal mucification method of Fluhmann for blood estrogen;<sup>10</sup>
- (3) The Venning-Browne gravimetric test for sodium pregnanediol glycuronide (an excretion product of progesterone) in the urine;<sup>36</sup>
- (4) Callow's colorimetric method for estimating urinary androgens.<sup>2</sup>

The Fluhmann FSH or thyliakentrin test deserves special mention; it requires at least 50 mouse units FSH per liter of blood to produce a positive test. It is usually positive in primary ovarian failure and negative in normal mature women. A positive test with a negative estrogen test denotes primary ovarian failure,<sup>11</sup> as in the climacteric. A negative reaction with a positive estrogen test indicates a responsive ovary, and a negative test along with a negative estrogen test indicates ovarian depression secondary to pituitary hypofunction.

#### MODERN CONCEPTS OF FEMALE ENDOCRINOLOGY

During childhood there are minute amounts of estrogen, androgen, and follicle-stimulating hormone of the anterior pituitary (FSH) (thyliakentrin) in the circulation and no progesterone. At puberty there is an increase in thyliakentrin and a resulting general stimulation of the primordial follicles of the ovaries to produce estradiol. Under the influence of estradiol, which is present in appreciable but variable concentration until

the climacteric, the secondary sexual characteristics develop and are maintained in their integrity. The first menstruations are anovulatory in most cases, endometrial degeneration and bleeding being due to fluctuations in estrogen production.<sup>27</sup> Rise in blood estrogen beyond a certain point depresses anterior pituitary function;<sup>28,35</sup> this in turn diminishes the stimulus to estrogen production. While under the influence of adequate estrogen, the endometrium goes through the proliferative phase, and when estrogen with its stimulus is withdrawn degeneration takes place.<sup>27</sup>

After a variable period of such cyclic bleeding or anovulatory menstruation, the adult ovulatory type of menstruation appears. During active menstruation, blood estrogen is at its lowest levels, and thyakentrin from the uninhibited anterior pituitary causes the growth of a primordial ovarian follicle and secretion of estradiol by its theca and granulosa cells during the postmenstrual and preovulatory periods. Endometrial repair and growth proceed under the influence of estradiol, and the follicle enlarges. At the time of ovulation the follicle ruptures, and there is a drop in blood estrogen content, following which there is occasionally a short period of intermenstrual bleeding. The organization of the corpus hemorrhagicum into the corpus luteum and secretion of progesterone is due to the influence of the luteinizing hormone of the anterior pituitary (LH) (metakentrin), which started its appearance just prior to ovulation. The corpus luteum is maintained in an active state for the production of progesterone by the lactogenic hormone (prolactin) of the anterior pituitary.<sup>5</sup>

Following the ovulatory phase drop, the concentration of estrogen again increases until the twenty-second day of the cycle, which is about the peak of progesterone concentration also. There is then a drop in the concentration of both, most rapid on the twenty-sixth day, due presumably to failure of stimulation from the reciprocally inhibited pituitary with consequent degeneration of the corpus luteum. Normal menstruation then follows on the twenty-eighth day, estrogen is at its lowest, and the uninhibited pituitary repeats the cycle.

If conception and implantation take place, the premenstrual drop does not occur. Instead, blood estrogen and progesterone increase, and chorionic gonadotropin appears. Chorionic estrogen and progesterone appear later. After parturition, chorionic hormones and progesterone disappear, estrogen levels drop, and the pituitary-ovarian cycle is resumed.

At the climacteric, the ovary is no longer responsive to thyakentrin stimulation with the growth of a follicle and production of estrogen. The climacteric phenomena can be ascribed to (a) an increased production of follicle-stimulating hormone from the uninhibited anterior pituitary or (b) a lack of estrogen. The evidence favors the former view, as inhibition by other means, such as testosterone, can relieve menopausal symptoms.<sup>31</sup> Occasionally, too, there are instances in which there may be some increase in blood estrogen following the cessation of menstruation.

The steroid hormones of the adrenal cortex are closely related chemically to the gonadal steroids and have some estrogenic properties, although it has been said that their androgenic effect may indirectly influence ovarian function. Certainly, the adrenal steroids may produce changes in the sex organs of either sex. The androgens may possess estrogenic<sup>4</sup> and progestational<sup>23</sup> qualities, and progesterone may have slight androgenic activity. To help complicate matters, estrin and progestin occur in the adrenals.<sup>3</sup> Since the female physiologic sex pattern, normal or abnormal, depends on the hormonal balance operating at the moment, and since the net effects can be achieved by various combinations of hormones, it inevitably follows that different authors have different explanations for the same clinical manifestation. The correctness of one explanation casts no reflection on the accuracy of another, since clinical material doubtless can be found to corroborate each.

#### PATHOLOGICAL ENDOCRINE PHYSIOLOGY AFFECTING THE ALLERGIC STATE

1. Hormonal patterns during puberty when not producing the usual anovulatory type of menstruation are characterized by their irregularity and unpredictability from month to month. Spontaneous adoption of a characteristic pattern is only a matter of time. The effect on the emotional state is the significant factor.

2. The patients with "premenstrual" allergic disorders are those with premenstrual tension or the milder grades designated as premenstrual distress. In the classical case of premenstrual tension the patient exhibits nausea, headache, fever, nervous tension, lower abdominal pains and back pains. These symptoms come on five to seven days before the onset of the period and end when menstruation begins. Blood estrogen determinations have shown that patients suffer from too much estrogen,<sup>12,22</sup> and no thyakentrin is demonstrable. The postovulatory or premenstrual blood estrogen concentration rises to a height which produces toxic manifestations, or, as Zondek has shown, these patients are "allergic" to their own endocrine products.<sup>38</sup> The ovarian steroids cause sodium retention and extracellular edema; in the brain this leads to headaches, in the skin to pruritus and urticaria, and in the gastrointestinal tract to distention, disordered peristalsis and vomiting.<sup>16</sup>

When the "premenstrual" group is tested intradermally with estradiol or estrone in oil (0.1 mg. in 0.1 c.c. oil) with a simultaneous oil control, a positive skin test is usually obtained. It is either papular or erythematous, usually coming on in three to five hours and persisting for at least a day. A passive transfer test with the premenstrual serum of a "premenstrual type" patient to a normal woman will give a positive test with estradiol, but the normal recipient's untreated site will not react to estradiol. The direct test could be interpreted as an index of the patient's tissue susceptibility to the irritant effect of estrogen rather than as an

index of allergy to it. The passive transfer test, however, could only have the latter significance.

The allergic difficulties of patients with premenstrual tension are aggravated by the high estrogen levels of pregnancy but end at the menopause.

3. The patients of the true "menstrual" type usually do not experience the onset or exacerbation of their allergic difficulties until the first day or two of menstruation, but occasionally may on the day before. There is ordinarily more or less nervousness, irritability, dysmenorrhoea, and abnormality of flow. Little or no fever is the rule. There is no increase in blood thyakentrin concentration, and blood estrogen levels are low. In this group neither the direct estradiol "sensitivity" test during the premenstrual or menstrual phase nor the passive transfer test with the premenstrual serum can be elicited. They are likely to improve during pregnancy but often change over to the "menopausal type" at the climacteric.

4. As previously stated, the high estrogen levels characteristic of pregnancy may be beneficial to the patient of the "menstrual" type who becomes pregnant and be detrimental to one in the "premenstrual" group. The abundant estrogen has been exonerated as a cause of the early toxemias of pregnancy, but other hormones of pituitary and ovarian origin are still suspect.<sup>6,7,29</sup>

The ovary's production of estrogen may be diminished by pituitary inhibition with testosterone, but the placental production is unaffected.<sup>17</sup> The same experiments can be interpreted to mean that estrogen of ovarian origin is neutralizable physiologically by testosterone, but estrogen of placental origin is not.

5. Although both increased blood thyakentrin levels and decreased blood estrogen levels are found in the climacteric, it is the former condition which is characteristic. The estrogen is usually absent or low, but occasionally may be increased (possible extra-ovarian source?). When high, there is likely to be menorrhagia.

#### RATIONAL THERAPY OF PITUITARY-OVARIAN DYSFUNCTION AFFECTING THE ALLERGIC STATE

*"Puberty Type"*—No hormonal therapy is indicated because there is no consistent hormonal pattern to modify. In the majority of cases the endocrine factor responsible for the production of allergic manifestations will disappear during the normal course of maturation. Only psychotherapy plus the usual allergic management is indicated.

*"Premenstrual Type"*—Restriction of sodium chloride and administration of ammonium chloride provide more or less control of the characteristic sodium retention and extracellular edema.<sup>16</sup> There is partial prevention of the effects of the excessive estrogen, but nothing is done toward neutralizing the estrogen or inhibiting its production. Results, when obtained, are rarely complete.

The use of progesterone, under the supposition that premenstrual tension was due to unantagonized estrogen consequent to deficient luteinization,<sup>22</sup> has not produced any spectacular results in the author's hands.

The observation that Vitamin B deficiency impaired the liver's ability to detoxify estrogen<sup>1</sup> with consequent high blood estrogen levels led to the use of Vitamin B complex for premenstrual tension. The author's observations in allergic individuals with premenstrual tension is that the effect is likely to be spectacular if there are clinical signs of vitamin deficiency present but will be equivocal otherwise.

Excellent results were obtained by the author with the administration of 10 mg. of methyl testosterone orally twice daily for ten days before the onset of the expected period. The male hormone depresses the anterior pituitary function, which in turn results in less production of estrogen by the ovary; a direct antagonism of androgen and estrogen is also a possibility.<sup>32</sup> When employing this mode of therapy, it is advisable to withhold it every fourth month to note progress.

Another promising treatment in the author's hands is the subcutaneous or intramuscular (latter preferred) "desensitization" to alpha estradiol compounds starting with the amount just failing to give a positive skin test. Succeeding doses ascending by geometric progression are given every two or three days until tolerance is reached. Whether this should be considered as a form of classical desensitization or merely physiological adaptation to increased estrogen levels is a moot point.

It is of interest to note that urticarial attacks occurring during the premenstrual period can be duplicated in the inter-menstruum by injecting serum taken during the premenstrual period.<sup>15</sup> This would point either to a specific hormone or a specific allergen present at the time as the cause of the symptoms. Treatment with premenstrual serum has not worked well.

*"Menstrual Type"*—The physiological preventative is a large dose of estrogen so timed as to prevent or buffer the exaggerated drop in blood estrogen just before and during the menstrual phase. Because timing is so important and oral absorption so erratic, a single intramuscular dose of estrogen, preferably one of the "natural" or estradiol series, is used. The author has found that it usually requires a dose of 1 to 2 mg. of estradiol dipropionate or benzoate administered two to four days before the estimated onset of the period. It is advisable to withhold such therapy every fourth month in order to note any tendency toward spontaneous improvement.

*"Menopausal Type."*—Here the indication is for the administration of estrogen by oral or parenteral route in amounts adequate enough to inhibit the anterior pituitary function and then gradually tapering off.

Initially, there is a tremendous variation in dosage. By the intramuscular route, for example, between 5,000 and 50,000 international units may be required two or three times weekly at the outset. The vagaries of the percutaneous and vaginal routes of administration render them unsatisfactory.

If menorrhagia is present without changes requiring surgery or radiation, one may use androgen to inhibit the anterior pituitary function and stop the bleeding.

During the menacme, in addition to the premenstrual and menstrual types of migraine, there is a type of migraine associated with spasmodic excess thylakentrin production. In spite of its occurrence in youth, its similarity to the menopausal type is striking. This type is preceded by a rise in gonadotropin in the urine followed by a drop on the first day of the seizure, and with little or no estrogen demonstrable.<sup>30</sup> In the majority, an injection of human chorionic gonadotropin will precipitate an attack. This kind of headache can occur at any time during the cycle, and these patients usually have similar headaches after the menacme. The climacteric may even aggravate the condition. It is the author's impression that these headaches are more likely to occur during mid-cycle, the only time that thylakentrin is ordinarily demonstrable in the blood and urine.<sup>33</sup> Estrogen therapy,<sup>33</sup> though logical, has not been completely satisfactory because of the obvious difficulty of timing. Continuous estrogen therapy would be illogical and possibly harmful.

*"Pregnancy."*—The relief afforded those patients of the "menstrual type" is gratefully accepted. Although the "premenstrual type" is aggravated by pregnancy, hormonal therapy is rarely indicated. Progesterone therapy, salt restriction, and Vitamin B therapy employed for such complications as toxemias, habitual abortion and threatened abortion can effect allergic manifestations if the patient is basically one of the "premenstrual" type. The successful use of testosterone therapy to inhibit the rate of production of skin pigment due to estrogen excess<sup>37</sup> suggests its cautious trial in severe allergic conditions with the same basis occurring during pregnancy.

#### RESULTS OF THERAPY

The effects of pituitary-ovarian dysfunction are most notable in migraine, urticaria and asthma, less visible in perennial allergic rhinitis, and hardly noticeable in seasonal allergic rhinitis and eczema. Patients with the last two disorders were not included in this study. Table I presents cases classified under allergic disorders. Table II regroups the same cases from the standpoint of endocrine dysfunction.

#### ALLERGY TO VEHICLES

The possibility that patients may be allergic to the oily vehicles used in parenteral preparations of androgens and estrogens must be con-

## SEX HORMONES IN ALLERGIC DISORDERS—HARTMAN

TABLE I.

Allergic Disorder and Subtype	Total Cases	Number Improved	Therapy Employed	Remarks
URTICARIA				
Menopausal	20	17	Estrogen in 18. Androgen in 2	(a)
Menstrual	19	17	Timed estrogen parenterally	
Premenstrual	9	3	Vitamin B Complex	(b)
Premenstrual	12	11	Methyl testosterone orally	
Premenstrual	10	7	Estradiol "desensitization"	
78 % Improved	70	55		
MIGRAINE				
Menopausal	18	14	Estrogen	
Menstrual	14	12	Timed estrogen parenterally	
Premenstrual	11	4	Vitamin B Complex	(c)
Premenstrual	7	7	Methyl testosterone orally	(d)
Premenstrual	3	3	Estradiol "desensitization"	(e)
75 % Improved	53	40		
ASTHMA				
Menopausal	24	22	Estrogen	
Menstrual	14	11	Timed estrogen parenterally	
Premenstrual	7	4	Methyl testosterone orally	(f)
Premenstrual	7	5	Estradiol "desensitization"	(g)
81 % Improved	52	42		
PERENNIAL ALLERGIC RHINITIS				
Menopausal	16	13	Estrogen	
Menstrual	7	5	Timed estrogen parenterally	
Premenstrual	2	2	Methyl testosterone orally	
80 % Improved	25	20		

(a) Two patients with menorrhagia treated with testosterone.

(b) No obvious clinical avitaminosis.

(c) Clinically avitaminotic.

(d) No obvious clinical avitaminosis. Had preceding treatment with Vitamin B Complex without results.

(e) Also had urticaria.

(f) Negative Estradiol skin test.

(g) Positive Estradiol skin test.

TABLE II.

Type	Total Cases	Number Improved
MENOPAUSAL		
Urticaria	20	17
Migraine	18	14
Asthma	24	22
Perennial Allergic Rhinitis	16	13
84 % Improved	78	66
MENSTRUAL		
Urticaria	19	17
Migraine	14	12
Asthma	14	11
Perennial Allergic Rhinitis	7	5
83 % Improved	54	45
PREMENSTRUAL		
Urticaria	31	21
Migraine	21	14
Asthma	14	9
Perennial Allergic Rhinitis	2	2
67 % Improved	68	46

sidered.<sup>25</sup> Peanut and cottonseed oils, commonly used for this purpose, are well-known allergens. Sesame, corn and olive oil allergies are much less frequent but do occur. Certainly, the possibility of allergy to the vehicle (about 4 per cent of women) should be considered before the

possibility of hormone allergy, and proper control tests made. Oral therapy or the parenteral use of aqueous suspensions are indicated in this vehicle-sensitive group.

#### PRECAUTIONS IN ENDOCRINE THERAPY

It would not be wise to close this paper on sex hormone therapy without mentioning some required precautions and the reasons therefor. Sex hormone therapy should not be employed unless there are definite indications and the clinical condition is of appreciable severity. A history of neoplastic disease or tendency thereto in the patient and her blood relatives should be obtained and carefully weighed. Examination of the pelvic organs and breasts in women should be performed before commencing endocrine therapy and should be repeated at appropriate intervals. Uncontrolled androgen therapy in women can lead to hirsutism, voice changes and menstrual changes. Protracted estrogen stimulation plays a part in the etiology and growth of uterine fibroids,<sup>26,37</sup> endometriomata,<sup>24</sup> cervical neoplasms<sup>14</sup> and uterine carcinomata.<sup>19,21</sup> The incidence of breast carcinoma is believed to be increased by prolonged estrogen stimulation.<sup>18,20</sup> In experimental animals, prolonged high-dosage estrogen treatment results in pituitary changes, characterized by the complete degranulation of the basophile cells, subtotal degranulation of the acidophile cells, and the formation of large chromophobic adenomata.

#### SUMMARY AND CONCLUSIONS

Allergic phenomena frequently cease or begin at puberty or the climacteric, and during the menacme they may be exacerbated during the menstrual or premenstrual period. At these times the usually satisfactory allergy regimes of elimination and desensitization may be relatively ineffective. The ways in which endocrine dysfunction may bring about clinical manifestations of allergy are listed. The aberrancies in pituitary-ovarian function in the groups of allergic patients under discussion are analyzed. Important factors determining the type of sex hormone therapy are: the time of appearance of clinical manifestations; the gonadotropic and steroid hormone inventory at that time; the presence of endogenous hormone sensitivity.

In general, allergies appearing at puberty should receive the usual allergy regime plus psychotherapy for the disturbed emotional state until some consistent hormone pattern is established. Menopausal onset or exacerbation is due to uninhibited pituitary overactivity, which may be inhibited by estrogen but also by androgen if bleeding is present. Satisfactory results were obtained in 84 per cent of this group. Menstrual phenomena are usually due to transient estrogen deficiency, which can be prevented in 83 per cent of cases by a single large properly timed injection of estrogen just before the expected period. Premenstrual exacerbations or appearances are usually associated with "premenstrual tension," the fundamental



difficulty being temporary estrogen excess with altered reactivity to same. This can be combated by oral methyl testosterone therapy during the postovulatory and premenstrual phase or by "desensitization" to estradiol, skin sensitivity to which can be demonstrated. Sixty-seven per cent of the "premenstrual" group responded satisfactorily to therapy.

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## MOLD FUNGI: MOLD EXTRACTS

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## LIGHT URTICARIA

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IT was Bazin<sup>5</sup> in 1855 who first called attention to the fact that sunlight, acting on a sensitive skin, can produce various types and degrees of reactions to it. Then came Anderson<sup>2</sup> who first introduced the thought that a photosensitizing substance might play a role in such cases. Later Duke<sup>15</sup> described illnesses, caused by sensitiveness to the action of physical agents, e.g., light, heat, cold, and mechanical irritation, as cases of "physical allergy." He mentioned two distinct varieties of physical allergy. In one type, the reaction is confined to the skin area directly exposed to the physical agent (called contact reaction); in the other type, the reaction may involve not only the skin areas directly exposed, but also distant tissues as well (called reflex-like reaction). He considered the contact type as comparable to the drug allergies, while the reflex type was regarded as probably caused by a disturbance of the heat-regulating mechanism of the body. It was Duke who called especial attention to the physical agents as causes of many cases of urticaria and angioneurotic edema, and sometimes also of such conditions as asthma, coryza, headaches and tachycardia.

The question as to whether sunlight urticaria is a genuine allergy, or whether it is only a photodynamic phenomenon has been discussed by many authors. Entering into this discussion has been the reported successful passive transfers with their implications of a true allergy.

The passive transfer of photogenous urticaria has raised the question of whether only reagents are transferred in the serum, which enters the cells of the test person, and become activated under the influence of the homologous light (a genuine allergy); or whether there is a transfer of an already known photosensitizing substance becoming active likewise under the influence of light (a photodynamic phenomenon). The theoretic difference between the two concepts consists in the fact that for the allergic theory, it presumes a reagent, put into action by the light and inducing urticaria through forming H-like substances. In contradistinction, a photodynamic chemical, e.g., porphyrin, et cetera, may be the photosensitized substance transferred, according to the latter concept. In this vein of thought, Rajka<sup>23</sup> believes that positive passive transfer is only possible in a specially strong hypersensitivity, i.e., at a high reagent titer of the blood, when the reagents, fixed in the cells, enter the circulation in an appreciable quantity.

In support of the first theory Sulzberger and Baer<sup>24</sup> obtained a positive passive transfer, and ascribed the urticarial sensitivity as due to the presence of an antibody (reagent) in the blood stream. They argued this point on the fact that (1) incubation of their patient's serum for one

hour at 60° C. abolished the capacity of the serum to transfer the light hypersensitivity to normal skin; (2) one full reaction-producing exposure of a passively sensitized site sufficed to exhaust its capacity to react; (3) no known photodynamic nor photosensitizing chemicals (porphyrins, et cetera) were demonstrable in their patient's serum; and (4) if not exposed, the sites of serum depot did not diminish in sensitivity to light, but gave maximum reactions four days or more after their injection into normal skin. For these reasons, they believed in the presence of an antibody (reagin) here.

Contrariwise, Epstein<sup>16,17</sup> emphasizes that while passive transfer in the sense of the Prausnitz Kustner phenomenon is always an expression of allergy, yet, in dermatoses due to hypersensitivity to light, the term passive transfer has been used in a wider sense indicating any form of transfer of such hypersensitivity from one person to another. This transfer, he stresses, does not necessarily imply allergy. A photosensitizing agent causing the patient's hypersensitivity to light may be present in his serum and in this way, account for the reaction on the part of the recipient. Such a mechanism, he believes, seems indicated in Callaway's<sup>13</sup> first positive passive transfer reported in this country. Another point Epstein makes is concerning the antigen itself. Ordinarily, in the Prausnitz Kustner phenomenon, antibodies from the patient's serum are transmitted to the test person. The positive reaction is elicited by subsequent injection of the antigen into the prepared site of the recipient. The mechanism of passive transfer in the photoallergic condition is the same in principle. The antibodies are transmitted with the donor's serum. Yet there is this difference. The antigen is not injected but must be produced at the recipient's site by the action of light upon the proantigen, and the latter must have been transmitted with the donor's serum.

Blum et al<sup>11</sup> in their case of a positive passive transfer demonstrated that the light absorber, which is constantly present in the patient's skin, and the light absorbers in the area of normal skin, photosensitized by passive transfer, have the same action spectra; and are therefore presumably identical. The wheals, too, are produced in the areas of passive transfer by the same wave lengths that elicit the urticarial response in the light-sensitive patient.

The various parts of skin of the body exposed to light have a definite effect on reactions produced by light, in these light-sensitive cases. Thus, Blum<sup>8</sup> showed by measuring the threshold times of various portions of the body, that their skin photosensitivity varied. The more exposed areas, e.g., the palm of the hand, the back of the hand and the cheek, were much more insensitive to light than, e.g., the abdomen or the back. In other words, parts of the body habitually exposed are considerably less sensitive than those usually covered by clothing.

The active site of the reaction that develops in photosensitivity, is believed to be close to the minute blood vessels in the papillary layer

of the skin.<sup>8</sup> The "burn" produced by ultraviolet light takes a few hours to appear and the longest wave length that can produce it is about 3150 Å°, with a maximum at 2967 Å°. Here, the erythema production takes place in the basal cells of the Malpighian layer and in the corium of the skin.<sup>20</sup>

Sir Thomas Lewis<sup>21</sup> demonstrated that the response of cutaneous vessels to mechanical, electrical, thermal or chemical injury is triple. There is (1) reddening due to capillary dilatation, (2) a mottled red flare with crenated edges, the result of arteriolar dilatation and (3) a wheal due to the increased permeability of the minute vessels which permits the escape of fluid in the tissue spaces. Histamine produces this typical "triple response" of Lewis. Hence, since the response of the skin, in urticaria solaris, resembles this triple response of Lewis, it is thought the rays of the sun liberate in the skin, histamine or a closely related H-substance.

H. Abramson<sup>1</sup> never found pseudopods develop even in 500 wheals produced as result of exposure to light. Hence, he believes the non-development of pseudopods is not in accord with the theory that a readily diffusible H-substance, like histamine, is liberated in the tissues subsequent to irradiation. He also demonstrated that a histamine wheal may be readily formed (by iontophoresis or injection) over an irradiated area of the skin which has responded, by whealing, to sunlight. In other words, the whealing response to light does not prevent histamine whealing in the same area. Similarly, a light wheal may be superimposed on a wheal formed by histamine iontophoresis. Thus, he argues that a histamine or readily diffusible H-substance is not responsible for the skin response to light irradiation. Duke<sup>14</sup> likewise found no tendency to spread, with pseudopod formation beyond the area exposed to the irritating agent, in his case further argument against the presence of a readily diffusible H-substance.

Contrariwise, Blum, Allington and West<sup>6</sup> noted the marked resemblance of the response of their patient to the triple response of Lewis. Thus, after exposure of the skin to sunlight, an erythema was first produced within a few minutes, limited to the area exposed. After a short time edema appeared, likewise restricted to the exposed area and still later an erythema developed, surrounding and spreading outward from the edematous area. After a few hours, no discoloration nor trace of the occurrence was found. Furthermore, no pigmentation developed. They further demonstrated that this photoresponse does not depend upon the presence of molecular oxygen.

Sulzberger and Baer<sup>24</sup> present the hypothesis that the change produced by light consists of the local conversion of a pre-urticariogenic substance into an urticariogenic substance or the liberation of an urticariogenic substance. This substance, formed or liberated, is nondiffusible, since the effect of irradiation is limited to the irradiated area. They found a

slight rise in the blood histamine level, and concomitantly, a slight rise in the free and total gastric acids, about twenty minutes after exposure to light. These findings suggest that histamine, or a histamine-like substance, is liberated or produced at some stage in the patient's reaction to irradiation.

Laurens<sup>20</sup> does not believe that porphyrins necessarily play a part in light sensitivity, but may represent products of skin injury, and be a result rather than a cause of dermal sensitization. This is stated because it has been noted that while porphyrins may sensitize the skin, e.g., in lead poisoning, porphyrins also have been found to be reduced in some cases of hydroavacciniforme. Also, light sensitivity may even be reduced when porphyrins are present in large quantities, in other cases of hydroavacciniforme. Callaway<sup>13</sup> reported an increase of coproporphyrin I in his case. Urbach and Shay<sup>25</sup> found only a slight increase in the stool and urine output of porphyrin. Anderson and Ayres<sup>3</sup> believe that sulphur metabolism plays a role in the production of light sensitivity. Porphyrins probably play little part in producing lesions of sunlight sensitivity.

In their experiments Blum and West<sup>7</sup> demonstrated that response to light obeys the reciprocity law, i.e., there is a reciprocal relationship between response, and the intensity and duration of irradiation. Also, the reaction which develops is not greatly affected by temperature. All parts of the body were found to be sensitive to light (with the usual variations found in habitually exposed areas, as contrasted to clothing-covered areas). Furthermore, there was not much fluctuation in sensitivity, during the course of ten months' study, showing the influence of time on light sensitivity.

#### CASE REPORT

The patient first presented herself for study at the age of thirty-five, in the spring of 1942. She gave a history of first developing itching and hives on exposure to sunlight at the age of twenty-five. She had consulted a variety of physicians and taken innumerable prescriptions and used various types of lotions to no effect.

Her previous medical history was completely negative. Menstruation began at the age of thirteen, occurred every twenty-eight days and lasted for three days, and tended to be on the scant side. Patient was always inclined to obesity. Unless she watched her diet carefully, she would gain weight quite rapidly.

At the time of the initial visit, a lotion containing pheynl salicylate, and tannic acid in alcohol was prescribed. No relief was obtained from the lotion. As patient lived out of town it was suggested further studies would be required.

The following year, in 1943, patient was admitted to the Jefferson Hospital for study. Her blood sugar and urea were within normal limits. Wassermann test was negative. Blood proteins were 7.7 mg. of which albumen was 5.6, and globulin 2.1, a normal ratio. The complete blood count and urine studies revealed no abnormality. No eosinophiles were found in the smear. The blood cholestrol was 228 mg. and the basal metabolism rate was minus 20. The free and combined urine estrogens were less than 6, and the combined were less than 5.

Examination of the patient revealed a well-developed woman, on the stoutish side, with no rash present on the body. There was some slight pigmentation

present of the exposed areas of the skin. Eye ground examination was negative, teeth were in good repair, tonsils were out and the thyroid was not enlarged. Heart and lungs were found normal and abdominal examination was negative. There were no aberrant reflexes.

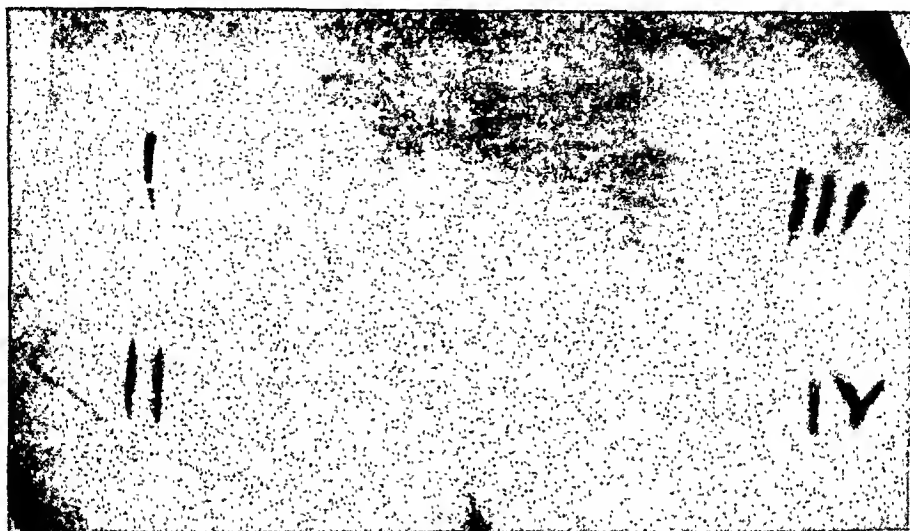


Fig. 1. The patient after exposure to (I) infra-red lamp at 30 inches for ten minutes, (II) hot quartz lamp at 30 inches for two minutes, (III) Kromyer ultraviolet lamp at 1 inch for thirty seconds, and (IV) Tungsten lamp. The photograph was taken about ten minutes after lamp exposures. The same exposures on a control patient, of the same age and hair-coloring, produced no reactions at all.

Exposure of the skin of the forearm to an ordinary summer's day sunlight for three to five minutes produced a hive corresponding in size to the area exposed. Around this would develop an intense red flare. There was no tendency for the hive to spread beyond the area exposed to sunlight, and the line of demarcation was quite sharp. On a summery day, with not too bright sun, it required about eight minutes' exposure to develop urticaria. Exposure to sunlight through ordinary window glass would produce urticaria also, but the time required to induce the reaction was increased by one and one-half to two times and, furthermore, the wheal itself was not as large nor the itching as intense as when no glass filtered the sunlight. Ordinary window glass, of the type that filters out rays below approximately 3200  $\text{\AA}$  was used. Gradually, the wheal and erythema faded and left no trace of its previous existence.

According to her history, this patient developed sunlight urticaria even in winter, although the symptoms were quite mild and a longer exposure was required. Blum et al<sup>9</sup> noted that where the urticarial response is elicited by a much larger fraction of sunlight, the patient suffers even in winter. The winter sunlight, while it does not contain as great a fraction of the sunburn-producing radiation rays as summer sunlight, does have waves that elicit an urticarial response almost as much as summer sunlight.

A fluorescent lamp failed to produce any erythema or urticaria in our patient. Blum<sup>12</sup> found that his patient developed some erythema, but no whealing as a result of exposure to fluorescent lighting.

Exposure to tungsten lamp, carbon-arc lamp, infra-red lamp, and x-ray failed to induce any reaction in the patient. Thirty seconds exposure to a Kromyer ultraviolet lamp at 1-inch distance (without filter) produced a prompt reaction in the patient within two and one-half minutes with development of a hive and erythema.

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Exposure to a hot quartz lamp for one minute at 30 inches produced a hive with erythema within three to three and one-half minutes (Fig. 1). Exposure of a control patient to the same lamps produced no reaction.

Intradermal skin tests were performed, and these proved essentially negative

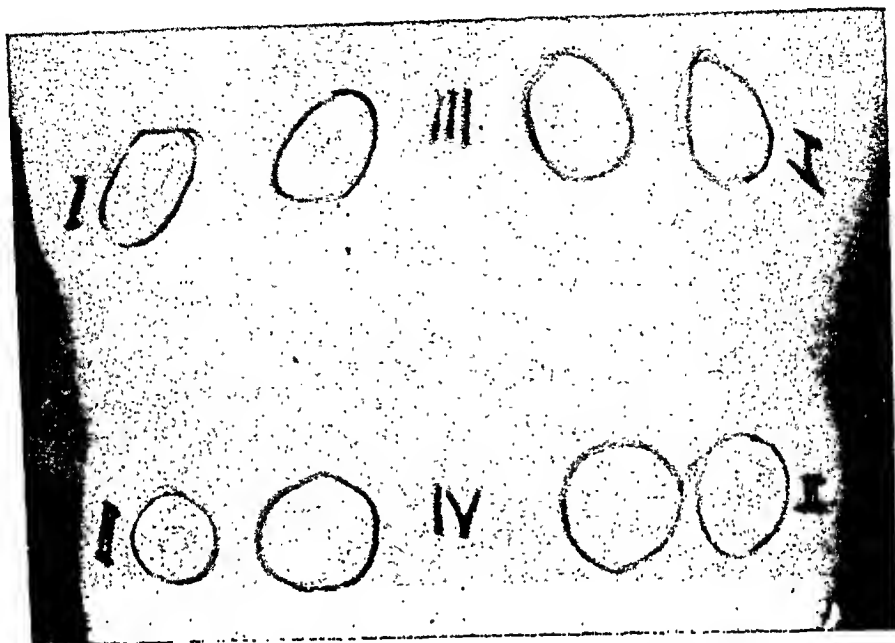


Fig. 2. Passive transfer in the control patient. On the left side of the spinal column are four sites prepared from serum of the sunlight-sensitive patient. On the right side are four similar sites prepared from serum of a nonsensitive donor. Sites I and II on the left responded to the Kromyer and quartz lamps, respectively, with the Kromyer giving the better reaction. There was no reaction in sites III and IV after exposure to infra-red and tungsten lamps, respectively. The sites on the right side, passively sensitized with normal serum, naturally showed no reaction to any of the lamps.

with the exception of moderate reactions to buckwheat, barley, and wheat. The patient stated that ingestion of cereals seemed to make her feet swell.

Estrogen in doses of 10,000 international units, three times weekly, along with thyroid extract, grains 3 daily, and a diet, low in fats, and cereal free, were prescribed.

The patient left the hospital and during the rest of the summer (July and August) continued her treatment with no relief.

In 1944, late in the winter, she began limited exposures to sunlight, first covering her skin with mineral oil, and continued this practice into the summer. She attained quite a tan that summer but despite this, failed to obtain more than slight relief. We know that pigmentation fails to protect these patients from their urticarial reaction the way it protects people from sunburn.

Urticaria solaris is not followed by pigmentation, and it is independent of oxygen.

At one point of her treatment, the patient, believing that her deep tan would protect her, lay on a seashore beach for half an hour in a bathing suit. She promptly lapsed into complete unconsciousness. Efficient treatment with large doses of adrenalin, and external warmth, revived her after a few hours.

In the spring of 1946, the patient was seen again, with a history of brief unconsciousness, as a result of fifteen to twenty minutes' exposure to the Florida sun. The patient had tried using a Hanovia sun lamp in increasing amounts, starting with very brief exposure, in an effort to build up her tolerance to sunlight. This



too had failed. A series of histamine injections, autohemotherapy, the use of crude liver extract parenterally, oral and intravenous administration of nicotinic acid or its amide, low protein and acidophilus culture diet, likewise failed to give any relief.

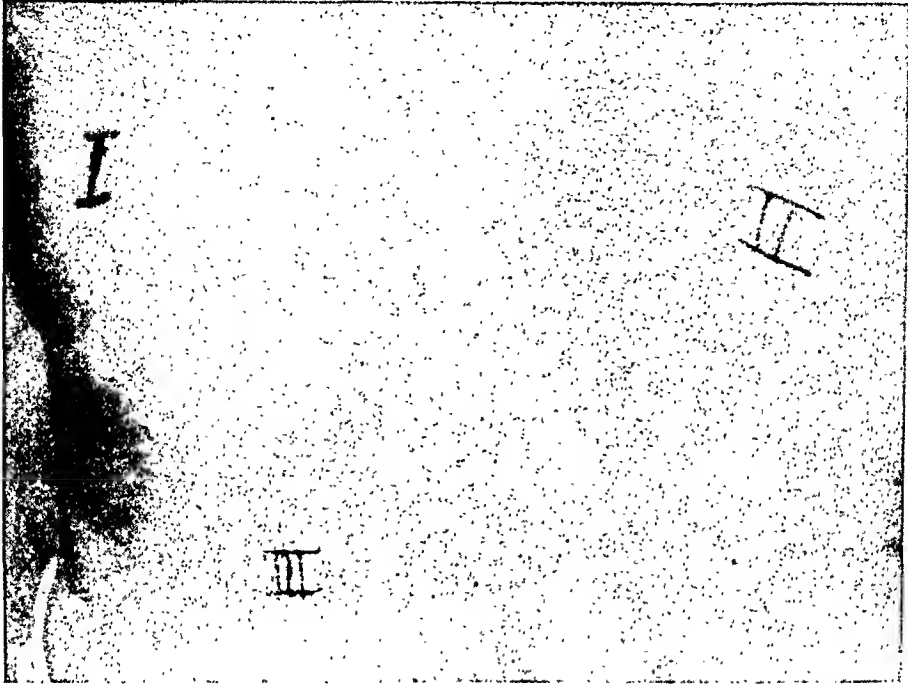


Fig. 3. The patient after exposure to a Kromyer lamp at 1 inch for thirty seconds, using three different filters, I, II, and III. Numbers I and III failed to give a reaction. Number II produced a hive with erythema, three minutes after exposure.

Passive transfer, which had been found positive in 1943, was done again. Controls, using both normal serum and saline solution, were negative (Fig. 2).

Under Dr. Lowell Erf's supervision, we attempted to see what effect autohelio transfusion would produce in the patient. A machine was used which irradiated every 10 c.c. of blood for one second with rays ranging from 2,800  $\text{\AA}$  to over 10,000  $\text{\AA}$ , with the majority of the rays being at 3,600  $\text{\AA}$ . At first only 10 c.c. of blood were withdrawn from the patient, irradiated in the machine, and then restored into the veins of the patient. Later 40 c.c. were tried and eventually 250 c.c. were used. At no time, as the result of this investigation, did the patient develop any hives, itching nor constitutional symptoms. Furthermore, there were no effects on her condition later on.

Filters to determine which rays were responsible could not be obtained. However, a few were obtained which managed to give us a fairly close idea of the range to which our patient was subject.

Figure 3 shows the patient after having used a Kromyer lamp on her skin at 1 inch for thirty seconds through three different filters. Numbers I and III failed to react. Number II gave a pronounced hive with erythema, about three minutes after exposure.

Filter No. II was a wine-colored Corning filter, No. 584, which has a range of light transmission between 3,550  $\text{\AA}$  and 3,750  $\text{\AA}$ . There is a steep rise to a peak of 3,650  $\text{\AA}$  and a steep fall to 3,750  $\text{\AA}$  (Fig. 4).

Filter No. I was a gelatin filter, No. 34, of a lavender or purplish color. This

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filter has a peak of 4,000  $\text{\AA}$ , but transmits to a minor degree between 3,000  $\text{\AA}$  and 5,200  $\text{\AA}$  (Fig. 4). It failed to produce the expected reaction.

Filter No. III was a greenish gelatin filter, No. 75, transmitting rays between 4,500  $\text{\AA}$  and 5,300  $\text{\AA}$ , with a peak at 4,900  $\text{\AA}$  (Fig. 4). It failed to produce a reaction.

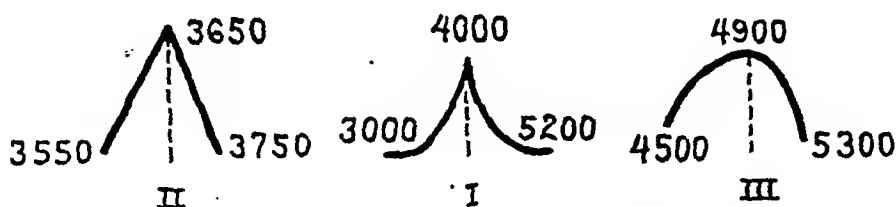


Fig. 4. Types of light transmission for filters used with Kromyer lamp as in Figure 3. Values are in Angstroms. Filter No. II produced a reaction.

The same tests were repeated using sunlight and a hot quartz lamp instead of the Kromyer lamp. The results were the same.

From the fact that our patient reacted to sunlight even through a window, although to a lesser extent, we may assume that rays above 3,000  $\text{\AA}$  are mainly responsible. The 'green filter, No. 75 (III), eliminated rays of 4,500  $\text{\AA}$ , as being responsible for the reaction. The results from filter No. 584 (II), definitely place most of the responsible rays at 3,550  $\text{\AA}$  to 3,750  $\text{\AA}$ . The results of filter No. 34 (I), are puzzling. Even though the peak is at 4,000  $\text{\AA}$ , the range should run down to 3,000  $\text{\AA}$ , which would permit the passage of some of the responsible rays. It is possible that not enough time was permitted to allow these diminished number of rays to pass onto the skin to provoke a reaction. If we assume that most of the rays come through this filter at the peak of 4,000  $\text{\AA}$ , we may believe our patient to be sensitive to rays approximately at a range not much more than 3,750  $\text{\AA}$  at the upper level, and probably close to 3,000  $\text{\AA}$  to 3,200  $\text{\AA}$  at the lower level.

### DISCUSSION

Our patient corresponds in her sensitivity to that described by H. Blum, Baer and Sulzberger<sup>11</sup> who found that positive passive transfers were found in their case where the causative wave lengths were below 3,700  $\text{\AA}$ . They differentiate their case from the one described by H. Blum et al<sup>12</sup> where the offending rays range between 4,000  $\text{\AA}$  and 5,000  $\text{\AA}$ . In the latter condition no positive passive transfer can be obtained. They believe these are two different diseases, although still urticaria solaris; but in the range of 4,000  $\text{\AA}$  to 5,000  $\text{\AA}$  sensitivity, passive transfer failure is typical of this disease.

Here we have a new concept as to the failure or success of passive transfer. It is the actual specific sensitivity to wave lengths above 4,000  $\text{\AA}$ , in a sensitive patient, that fail to give a positive passive transfer. This is contrary to the views previously expressed by Rajka<sup>23</sup> who believed that positive passive transfer was only possible in a specifically strong hypersensitivity, i.e., at a high reagin titer of the blood where the reagins enter the circulation in an appreciable quantity.

Patient was then given benadryl, 50 mg. three times daily, for two weeks. It had a definite effect on her skin, reducing the amount of itching

and hives produced, and increasing her tolerance to sunlight. The effect, however, was not appreciable enough to overcome the disadvantages of drowsiness produced by the medication. At best, only about 20 per cent relief was obtained. Hence, it was discontinued. Pyribenzamine was used, without results.

Hapamine was used by Blum et al<sup>11</sup> with no effect.

H. Arnold<sup>4</sup> obtained no results with torantil in a light-sensitive case.

V. Notier<sup>22</sup> found about 50 per cent improvement after the use of benadryl in a case of cold urticaria, but the degree of improvement began to decrease two weeks after discontinuance of the treatment. His patient received 50 mg. benadryl four times a day for eighteen days.

Urbach and Shay<sup>25</sup> emphasized the fact that treatment of a hepatopathy and gastrointestinal disease may relieve a light-hypersensitive case. However, the case they describe with marked improvement of light-hypersensitivity as a result of cholecystectomy, responded slowly to sunlight, was well in the fall of the year, and the symptoms seemed to be more of a reddening of the skin, with swelling and inflammation developing after two hours, than the prompt hive developed in our case.

Lancaster<sup>19</sup> treated his cases of photogenic eczema and dermatitis with estrogen (and thyroid) with excellent results. Hadley<sup>18</sup> likewise found that injection of estrogen gave almost entire relief in his case of urticaria solaris.

However, our patient remained intractable to all forms of treatment. She does notice that she can stand sunlight better if she is near a large body of water. Also, she is a trifle better after tanning and repeated exposures in small doses to the sunlight or sunlamp. The application of a lotion or powder, which would filter out her offending rays only, i.e., at a range of approximately 3,000 to 3,750 Å° would seem to be the most logical and easiest form of treatment.

#### SUMMARY

1. The history and development of sunlight urticaria is reviewed. The controversy as to whether it is true allergy or only a photo-dynamic phenomenon is discussed. The role of successful passive transfer in this controversy is mentioned.

2. A case of sunlight urticaria, with sensitivity to rays of approximately 3,000 to 3,750 Å° and with successful passive transfer, is presented.

3. The concept of Blum, Baer and Sulzberger, that positive passive transfer can be elicited only in patients sensitive to rays below 3,700 Å° is corroborated.

4. The failure of all agents to relieve the patient is noted.

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319 South Fifteenth Street, Philadelphia, Pennsylvania.

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## STATE LEGISLATION AGAINST DOG STEALING

State legislation against dog stealing passed this year in Massachusetts and New York and pending in California, Maryland, Wisconsin, Pennsylvania, and Michigan has been labeled a propaganda trick of the antivivisection cult by Dr. Anton J. Carlson, president of the National Society for Medical Research.

"For more than 100 years it has been illegal in most parts of the western world to steal dogs," said Dr. Carlson. "This new legislation adds nothing to the protection afforded pet owners by existing laws. The only reason for the introduction of these bills has been to provide a springboard for fantastic charges by the antivivisectionists against medical and veterinary institutions."

"It seems impossible," said Dr. Carlson, "that any one could believe that universities, state and city health departments, and great hospitals would sponsor thievery. Yet," Dr. Carlson observed, "it seems that some people will believe even the most ridiculous things if they see them in print."

Dr. Carlson suggested that the best way to protect pets would be to centralize all responsibility for the administration of laws pertaining to animals in a single government agency such as the police department. "Then," said Dr. Carlson, "the pet owner would always know where to turn for help in locating a lost animal."

"From the standpoint of medical research the advantage would lie in eliminating the confusion which makes antivivisection slanders possible," said Dr. Carlson.

# SPONTANEOUS FRACTURE OF THE FIRST RIB AS A COMPLICATION OF STATUS ASTHMATICUS

MATTHEW GINSBURG, B.S., M.D., F.A.C.A.

Toledo, Ohio

THE usual complications of chronic asthma are found within the confines of the thoracic cage. Rarely does one encounter a spontaneous fracture of the rib as a result of asthma. The rarity of the above finding is attested to by the fact that no cases were found in a search of the literature, yet it is almost certain that some must have been reported.

## CASE REPORT

The patient, an adult white woman, fifty-nine years of age, was admitted to the hospital March 2, 1946, in status asthmaticus. She was discharged on March 29, 1946, slightly improved. During childhood and again at the menopause, she had had repeated attacks of asthma. Six months before the present admission, asthma recurred and remained persistent. She had been in another hospital for status asthmaticus for seven weeks and had improved before discharge. There was an interval of four weeks during which she was fairly comfortable preceding the present attack. The ingestion of quinine produced hives, and aspirin caused vomiting. For many years, she had had nasal polypi. One sister had asthma.

Physical examination revealed an emaciated white woman in extreme respiratory distress. She sat up in bed supporting herself with her hands by her sides. The accessory muscles of respiration were prominent. Sweating was profuse. The blood pressure was 120/84. Temperature was normal. Auscultation of the chest revealed the usual asthmatic rales. The sputum was thick and mucoid. Blood counts and urinalyses were within normal limits. She complained of aching pains in the right side of the neck, which first began shortly before the present admission to the hospital. An x-ray of the neck and upper chest revealed the presence of a recent fracture of the left first rib, 2 inches from the spinal column (Fig. 1). The location of the pain did not fit in with the site of fracture so a repeat x-ray was ordered, and again the left first rib was reported as fractured. It is difficult to account for the pain being on the right side when the fracture is on the left, unless it is referred. The patient gave no history of an injury or fall.

A review of the anatomy<sup>2</sup> of the thoracic cage and the physiology<sup>1</sup> of respiration is apropos at this time. The first rib is flat and not twisted. The muscles attached to the superior surface are the scalenus anticus and medius and the serratus magnus. The external intercostal muscle is attached to the inferior surface. There is a fairly deep groove between the scaleni muscles wherein lies the subclavian artery; this, therefore, is structurally a weak point. The scaleni muscles raise the first rib during inspiration. The thoracic lid is formed by the first pair of ribs and the manubrium sterni. It is joined posteriorly to the spinal column and anteriorly to the sternum by the manubrio-sternal joint. During elevation of the thorax, in inspiration, the thoracic lid moves as a single piece upon the body of the sternum, assuming a more horizontal position. The manubrium is pushed forward and upward. The extent of the upward move-

ment varies in different individuals and with the depth of inspiration. Elevation of the ribs is effected by the external intercostal muscles, the fibres of which pass obliquely downward and forward from the inferior border of one rib to the superior border of the rib below. When the



Fig. 1. Arrow indicates fracture of left first rib.

muscle contracts it exerts a pull upon these attachments which tends to depress the upper rib of the pair and raise the lower. The first rib, however, acts through the contraction of the scaleni muscles as a fixed point above, so that contraction of the external intercostals can only result in an elevation of the ribs.

It is conceivable that contraction of opposing muscles, i.e., the scaleni above and the external intercostals below, was enough to fracture the first rib.

## SUMMARY

Spontaneous fracture of a rib occurring in asthma is rare. Violent, persistent contraction of opposing muscles is offered as a possible explanation.

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# ALLERGIC DERMATITIS FROM VAGINAL ABSORPTION OF SENSITIZERS (Floraquin and Verazeptol)

## Report of Cases

BOEN SWINNY, M.D., F.A.C.A.

San Antonio, Texas

THE cause of a considerable number of cases of dermatitis has been overlooked because of failure, in taking the drug history, to inquire specifically about the use of douches and suppositories. Patients are prone to overlook these when asked what drugs they are taking, as they think only of those ingested.

Floraquin suppositories (diodoquin, 5, 7-diiodo-8-hydroxyquinoline) are widely used in the treatment of trichomonas vaginitis. Verazeptol powder, containing chlorthymol, eucalyptol, menthol, phenol, zinc sulphate and boric acid, is widely used in cleansing douches. Search of the literature has revealed no previous reports of sensitivity to either of these preparations. Gaul<sup>1</sup> has reported a case of dermatitis medicamentosa from the intravaginal use of Floraquin. In his case contact test with Floraquin was negative.

### CASE REPORTS

*Case 1.*—Mrs. J. R., aged thirty-five, with areas of pruritic maculopapular eruption about her scalp margin and the "V" of her neck, of two weeks' duration, had been using Floraquin suppositories prescribed by her physician for trichomonas vaginitis one month before. A contact test with Floraquin after twenty-four hours gave a positive reaction duplicating the original lesions. Because of the possibility that this reaction was irritative, contact tests were done on three normal controls; there were no reactions in the controls.

*Case 2.*—Mrs. F. A. K., aged thirty-five, had a pruritic maculopapular dermatitis across the epigastrium and over the inner aspects of both mid-thighs, of three years' duration. The food, drug and environmental history gave no clues, except she was aware that she was sensitive to ammoniated mercury ointment, which was confirmed by a patch test with the 2 per cent ointment. Other contact tests were done with rayon, wool, nylon, soap, zinc sulphate, nickel sulphate. A strong positive reaction was obtained with zinc sulphate 5 per cent, with negative reactions to the others. In searching for exposure to zinc and mercury, we finally uncovered the fact that she had been using Verazeptol douche powder for many years. A contact test with Verazeptol 10 per cent was positive on her and negative on three controls. The other substances, chlorthymol 1 per cent, eucalyptol 1 per cent, menthol 1 per cent, phenol .25 per cent, boric acid (saturated solution) present in Verazeptol gave negative tests. Ten days after ceasing the use of Verazeptol, the skin cleared and has remained clear in three months.

### COMMENT

Although the vagina in both cases was the organ of absorption of the sensitizers, the mucous membrane in each case was entirely normal.

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# Department of Clinical Pathology and Laboratory Procedures

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## THE COMPARATIVE DIAGNOSTIC EFFICIENCY OF THE SEDIMENTATION RATE AND THE WELTMAN REACTION

L. O. DUTTON, M.D., F.A.C.A.

El Paso, Texas

FOR some time we have been determining the sedimentation rates and Weltman reactions almost routinely in the study of allergic patients. A note was recently published in the *ANNALS OF ALLERGY* concerning the technique and interpretation of the Weltman reaction.<sup>1</sup> It has been our impression that there is close agreement between the two tests, in a positive direction, in those patients who obviously suffer from infection. Likewise in a group of patients who obviously suffer from a simple and uncomplicated allergy, there is close agreement in the negative direction.

There has been, however, a middle group of patients in whom there was considerable doubt as to the presence or absence of infection or allergy, or the relative importance of the two if they existed simultaneously. In an effort to evaluate the relative efficiency of these two tests in this group of borderline patients, they were subjected to rather careful study and continued observation subsequent to treatment. All of these patients had been referred in an effort to determine their allergies since a clinical diagnosis had previously been made. There were forty-three patients in this group. The diagnosis of hay fever was made in thirteen instances, asthma in twenty-six instances, gastrointestinal allergy in two instances and chronic urticaria in two instances. These referred patients had received previous treatment of some kind, and the majority had been subjected to an allergy investigation.

The actual clinical existence of an infection in these patients was established by history, complete physical examination, cytological study and culture of the sputum and/or the nasal secretions, x-rays of the chest and sinuses and other organs when indicated, as well as their clinical course and response to therapy. By these methods it was established that of this group of forty-three individuals, thirteen showed symptoms whose causative factors were considered entirely of an allergic nature. Ten of the forty-three apparently suffered from an infection only. Seventeen were considered as chronic allergies with a superimposed infection. The sedimentation rates and Weltman reactions in these respective groups were as follows: (Sedimentation rates of more than 20 millimeters in one hour and Weltman bands of less than 6 were considered abnormal.)



## CLINICAL PATHOLOGY AND LABORATORY PROCEDURES

*Group 1.*—Allergic manifestations only—thirteen individuals. High sedimentation rate, exudative Weltman—no cases. Normal sedimentation rate, exudative Weltman—two cases. High sedimentation rate, normal Weltman—five cases. Normal sedimentation rate, normal Weltman—six cases.

*Group 2.*—Individuals exhibiting infection only—ten individuals. High sedimentation rate, exudative Weltman—six cases. Normal sedimentation rate, exudative Weltman—four cases. High sedimentation rate, normal Weltman—no cases. Normal sedimentation rate, normal Weltman—no cases.

*Group 3.*—Individuals exhibiting both allergy and infection—seventeen individuals. High sedimentation rate, exudative Weltman—ten cases. Normal sedimentation rate, exudative Weltman—six cases. High sedimentation rate, normal Weltman—one case. Normal sedimentation rate, normal Weltman—no cases.

*Group 4.*—Unclassified cases—three individuals. High sedimentation rate, exudative Weltman—no cases. Normal sedimentation rate, exudative Weltman—three cases. Normal sedimentation rate, normal Weltman—no cases. High sedimentation rate, normal Weltman—no cases.

Upon examination of these results, it will be seen that in Group 1 (allergic individuals only) the Weltman reaction showed an exudative reaction in only two cases. In both these the degree of the reaction was only slight, one having a Weltman band of 5 and the other a Weltman band of  $5\frac{1}{2}$ . In the remaining eleven individuals the Weltman reaction was completely normal but the sedimentation rate showed an increased rapidity of 20 millimeters or more in five. The cause of the increased sedimentation rate in five of this group is not clear since there was no demonstrable infection or other condition to explain it. Obviously entire dependence upon the sedimentation rate without simultaneously determining the Weltman reaction would be misleading.

In the second group of ten patients or those apparently with infection only, six showed an increased sedimentation rate and a positive Weltman reaction (most of the bands being in the region of 2, 3 and 4). In four the sedimentation rate was normal, although the Weltman reaction showed a definite exudative phase with a reading less than 6. In this group there were no Weltman reactions that did not confirm the clinical diagnosis. However, there was a normal sedimentation rate in four, and dependence on this test alone would have been misleading.

Of the third group of seventeen patients who manifested both infection and allergy, ten showed an agreement between the sedimentation rate and the Weltman reaction. The sedimentation rate was rapid and the Weltman reaction well below 6. Six had a normal sedimentation rate but an exudative Weltman reaction. In this group the sedimentation rate alone would have been misleading, whereas the Weltman reaction in one would have been deceiving. None in this group had both a normal sedimentation rate and normal Weltman reaction.

There were three unclassified cases, all of whom showed a normal sedimentation rate and a slightly exudative Weltman reaction, the values being 5 or  $5\frac{1}{2}$ .

(Continued on Page 494)

# Editorial

*The opinions expressed by the writers of editorials in the ANNALS do not necessarily represent the group opinion of the Board or of the College.*

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## FURTHER COMMENT ON DRUGS CLASSIFIED AS ANTIHISTAMINICS

Previous comments in these columns have emphasized the fact that drugs classified as antihistaminics, such as Benadryl and Pyribenzamine, have profound hypnotic effects. The clinical results, therefore, are not unequivocal as far as their antihistaminic action is concerned. Further data published in recent months by Levy and Seabury show that spirometric studies performed on sixteen patients, thirty minutes and one hour following the administration of 100 mg. of Benadryl orally, reveal no consistent tracings in the vital capacity, tidal air, minute ventilation, expiratory differential, respiratory rate or degree of emphysema. However, following the administration of epinephrine and aminophylline to five of these sixteen patients, there was a uniform increase of vital capacity, tidal air, minute ventilation, expiratory differential without any increase in the respiratory rate. Although six of the patients derived subjective benefits with decrease in dyspnea following the use of Benadryl, it is well known that sedation may produce the same effect. Indeed, in three of these patients with subjective benefit, spirometric data were directly opposed to the subjective reports. Further evidence that the so-called antihistaminic effects are not connected with the allergic state is to be found in the report of Schiller and Lowell. Brown and his co-workers had shown that a reduction in vital capacity occurs during the pollen season in cases of hay fever. Schiller and Lowell studied the reduction in vital capacity following inhalation of nebulized extracts of pollen in certain asthmatic subjects. These changes in vital capacity can be readily reproduced. The symptoms and signs which accompany such reductions in vital capacities resemble in many respects naturally occurring asthma. Schiller and Lowell dealt with the effect of adrenaline, aminophylline, atropine and Pyribenzamine on the modification of the reaction to inhaled pollen extracts as measured by changes in vital capacity. The effectiveness of the drugs studied in preventing or relieving induced reductions of vital capacity corresponds well with the known effects of these drugs in relieving spontaneously occurring asthma. The tests done with atropine and Pyribenzamine were of special interest. For example, in one patient it was shown that neither Pyribenzamine nor atropine influenced the reaction to inhaled pollen although the reduction in vital capacity following the inhalation of histamine was readily prevented by Pyribenzamine. The results of Schiller and Lowell indicate

that neither histamine nor acetylcholine play a determining role in the production of pollen asthma in the particular subject studied.

Most significant is the report of Guy on the effect of Pyribenzamine on the tuberculin reaction in man. Four hundred mgs. of Pyribenzamine per day were administered to five subjects, and the effect of tuberculin on the skin was studied following the injection of old tuberculin. Only those subjects who showed no significant degree of variation in their response to three consecutive series were selected for studies of Pyribenzamine. One hour before the injection of the tuberculin, 150 mgs. of Pyribenzamine were given to each subject by mouth. During the forty-eight hours following the injection, each subject received a total of 650 mgs. of Pyribenzamine in divided doses. The results showed unequivocally that there was no regularly significant effect on the degree of response to the tuberculin.

All of these data indicate that the use of Benadryl and Pyribenzamine as antihistaminics may well be justified where it is quite certain that histamine is the causative agent. However, in many allergic reactions, such as pollen asthma and the tuberculin type of skin reactions as indicated in the foregoing, the use of Benadryl and Pyribenzamine must be on a different basis. If it is desired to employ these drugs because of their hypnotic effects, we should certainly do so. We must understand, however, that we are not using the drugs as antihistaminics but as hypnotics. If we recognize this fact and use these drugs for their hypnotic action, the rationale of the procedure is based on logic, not on the histamine theory, the basic structure of which is extraordinarily weak in so many respects.

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## CLINICAL PATHOLOGY AND LABORATORY PROCEDURES

*(Continued from Page 492)*

From these observations it would seem that the Weltman reaction is somewhat more efficient than the sedimentation rate as a diagnostic aid. This is particularly true in borderline cases. We believe that these two tests, the Weltman reaction particularly, are valuable aids when determining those patients who have either a primary or complicating infection.

### REFERENCE

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# \* In Memoriam \*

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## ALFONSO GRANA, M.D., F.A.C.A.

We announce with sadness the sudden death of Alfonso Graña, August 26, 1947, at Montevideo, Uruguay.

Alfonso Graña was born in Rocha, Uruguay, on June 3, 1912. He graduated from the Montevideo University High School in 1932 and from the Medical School of the University of Montevideo in 1940. He took postgraduate studies at the Allergy Clinic in the Allergy Center of the Clinical Hospital of Buenos Aires in 1941 and did experimental allergy in the Institute of Biology in Sao Paulo, Brazil, in 1944.

Doctor Graña was Chief in Internal Medicine, Faculty of Medicine, Montevideo, Uruguay, 1941-1944 (Clinic of Professor J. C. Garcia Otero). He was also Chief of the Nutrition Clinic, Department of Allergy (Clinic of Professor Beguino Varela Fuentes), Montevideo, Uruguay, Faculty of Medicine.

Doctor Graña was appointed Assistant at the Institute of Experimental Medicine of the Mayo Foundation, Guggenheim Fellowship in 1945. At the Mayo Foundation he worked under the direction of Drs. F. C. Mann and H. E. Essex. One of the articles giving the results of his experiments at the Mayo Clinic, "Experimental Purpura and Pancreatic Necrosis Produced by Forssman Heterophil Antibody," was published in the Proceedings of the Staff Meetings of the Mayo Clinic (21:298, 1946). Another article, "Blood Platelets in Heterophil Anaphylaxis," was published in the Proceedings of the Society of Experimental Biology and Medicine (61:192-195, 1946). He also read a paper before the annual meeting of the American College of Allergists in San Francisco, June 28, 1946. This paper, entitled "Influence of the Liver in Anaphylactic Shock and Experimental Study," appeared in the ANNALS OF ALLERGY (4:261, 1946). Altogether, Doctor Graña published ten papers on hydatid allergy, four papers on anaphylaxis and two books. He co-authored "Alergia en la Practica Clinica" with Professor B. Varela Fuentes and Dr. R. P. Recarte (Espasa-Calpe, Argentina, S. A., Buenos Aires—Mexico, 1946).

Doctor Graña had many friends in the United States, both in the College and at the Mayo Clinic, where he was held in esteem for his experimental researches of a fundamental nature. Doctor Graña was unmarried. His many friends in the United States join in the sorrow of his colleagues in South America.

F.W.W.

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## SOUTHEASTERN ALLERGY ASSOCIATION

The third annual meeting of the Southeastern Allergy Association will be held in Richmond, Virginia, on January 17 and 18, 1948, at the Jefferson Hotel.

The president of the Association is Dr. J. Warrick Thomas, 201 W. Franklin Street, Richmond, Virginia and the secretary-treasurer is Dr. Katharine B. MacInnis, 1515 Bull Street, Columbia, South Carolina.

SEPTEMBER-OCTOBER, 1947

# News Items

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## 1948 MEETING OF THE AMERICAN COLLEGE OF ALLERGISTS

The Fourth Annual Meeting of the American College of Allergists will be held at the Hotel Pennsylvania, New York City, Friday, Saturday, and Sunday, March 12, 13, and 14, 1948. Members will soon be receiving room reservation cards for the Hotel Pennsylvania, and are urged to fill in these cards and mail them immediately, as all reservations will be made directly with the hotel by those attending this meeting.

There will be no scientific or industrial exhibits. The three days will be devoted entirely to an intensive scientific program with panel discussions as formerly. There will be no charge for registration. The Registration Desk will be open on Thursday afternoon, March 11. Everyone is welcome, both members and non-members, but all must register upon arrival and receive their badges. All Fellows and Associate Fellows must present their membership cards at the desk. There are no scheduled luncheons—the Annual Banquet will be held on Saturday evening, March 13.

Plans are being formulated by the Program Committee for three topics which will bring to focus certain important aspects of allergy at this time. As usual, these topics will embrace controversial subjects, about which a good deal, however, is known. They are: (1) Mold Allergy; (2) Rhinolaryngological Allergy; (3) Neuro-Allergy.

It is of special importance to note that the third topic, Neuro-Allergy, will be the subject of intensive research during the coming year. It is with a good deal of pleasure, therefore, that the College announces specific plans for the presentation of scientific developments along this line.

The Program Committee urges all Fellows and Associate Fellows who plan to submit papers for consideration to do so by December 1, 1947. Papers should be sent to Dr. Harold A. Abramson, 133 East 58th Street, New York 22, New York. It is necessary to have them in by December 1 in order that the program may be published in the *ANNALS OF ALLERGY*. All papers should be sent in duplicate, 250 words in length abstracted. Papers may also be presented *by title*. There is no limit to the papers *by title* which anyone can submit and be assured of their publication in the *ANNALS*, if accepted. However, only one paper of this type from each author may be presented at the meeting. All papers presented *by title* will appear as part of the regular program, thus assuring the author priority. Abstracts of the papers presented *by title* will be published in the *ANNALS*, with the papers which are actually given at the meeting. Presenting a paper *by title* does not obligate the author to attend the meeting.

All members have received a card for membership recommendation. Names proposed for Fellowship should be mailed to the office of the Secretary. Associate Fellows may also propose membership. Application blanks will then be mailed to those whose names are submitted, the forms to be filled out and returned, together with the recommendation of a sponsor and two other letters of endorsement.

### Requirements for Active Fellowship

The requirements for Active Fellowship and for promotion to Active Fellowship are:

1. All candidates must have been graduated from a reputable medical school for at least five years.
2. The candidate must furnish evidence of having applied proper allergy procedures to his practice for at least three years.

3. Evidence must be furnished of proficiency as practitioners, teachers, or research workers in organized branches of medicine, or in the field of allergy.

4. Published original works on allergy or allied subjects, or evidence of research in allergy now in progress but not yet published.

5. Evidence of training in allergy in out-patient clinics and hospitals or in the private clinic of the well organized specialist in allergy.

Associate Fellows—Any Associate Fellow seeking Active Fellowship must meet at least three of these requirements. Those who believe that they have these qualifications should submit them, together with evidence of work done satisfactorily, before being elected to Associate Fellowship. Those seeking promotions should send additional qualifications to the Secretary one month before any meeting of the Board of Regents, or one month before the Annual Meeting.

#### Sustaining Members

An interesting feature of membership now successfully launched by the College is a group known as Sustaining Members. A very substantial list of Sustaining Members will soon appear in each issue of the *ANNALS OF ALLERGY*. The establishment of a sustaining membership has been the custom of a number of scientific organizations for some time. For instance, the Society of American Bacteriologists publishes a list of seventy business concerns in their official organ, the *Journal of Bacteriology*.

The majority of these business firms, which include the manufacturers of drugs, pharmaceuticals, biologicals, scientific apparatus, and other products of interest, directly or indirectly, to the allergist or immunologist, now have well-organized staffs of research workers composed of some of the most outstanding scientists in their fields. With the best of equipment and co-ordination, these laboratories are contributing invaluable information and aid to the physician in all specialties and are ready to co-operate with the individual engaged in private research or with medical societies. It is logical that these firms associated with the allergists, both in a business and a co-operative way, be recognized as Sustaining Members.

All Sustaining Members will be listed in each issue of the *ANNALS OF ALLERGY*. They will also receive subscriptions to the *ANNALS OF ALLERGY* for their libraries. Members of their scientific staffs may attend the annual meetings of the College and may present a paper upon approval by the Program Committee. Sustaining members will also be listed in the programs of Annual Meetings and will be given priority for space and location at any scientific exhibits of any College meeting. A committee appointed by the Board of Regents passes upon the eligibility of Sustaining Members. Annual dues for a Sustaining Member is \$50.

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#### AMERICAN SOCIETY OF OPHTHALMOLOGIC AND OTOLARYNGOLOGIC ALLERGY

The American Society of Ophthalmologic and Otolaryngologic Allergy held its annual meeting at the Palmer House, Chicago, Illinois, Saturday, October 11, 1947. This meeting was dedicated to the President and Founder of the Society, Dr. French K. Hansel, F.A.C.A., St. Louis, Missouri. Dr. Hansel presented two papers; namely, "Skin Testing and Evaluation" and "Results of Clinical Investigation of Oral Ragweed Therapy." Dr. Fred W. Wittich of Minneapolis was elected the first Honorary Fellow of the Society.

During the 1946 meeting of this Society in Chicago, a group of its members proposed and adopted the plan of establishing the Hansel Foundation. In February, 1947, a charter was granted to the Foundation by the State of Missouri. The object of the Foundation is to promote further education and research in this special field of allergy. The Society already has seventy-eight members, and the interest, support and enthusiasm which have been exhibited by the members assure

the prospect of fulfillment of the aims and purposes of the organization. The officers of this Foundation include Dr. French K. Hansel, F.A.C.A., Director; Dr. W. Byron Black, F.A.C.A., President; Dr. Rea E. Ashley, Vice President; and Dr. Walter E. Owen, F.A.C.A., Secretary-Treasurer.

#### INTERNATIONAL ASSOCIATION OF ALLERGISTS

Dr. Paul Kallós, Helsingborg, Sweden, who is a member of the Executive Committee of the International Association of Allergists, has just completed a trip through Holland and Switzerland in behalf of the Association. As a result of Doctor Kallós' trip and recommendations, the Executive Committee of the International Association of Allergists has elected the following scientists in Switzerland to Active Fellowship in the Founders Group.

Prof. W. Löffler, Medical Clinic, University Hospital, Zurich.

Prof. W. Lutz, Dermatological Clinic, University Hospital, Basel.

Prof. A. Grumbach, Bacteriological Institute, Gloriastrasse 32, Zurich.

Prof. A. Gigon, Schweiz. Akademie f. Med. Wissenschaften, Hebelstrasse 1, Basel.

Prof. K. Bucher, Pharmacological Institute, University Hospital, Basel.

Asst. Prof. E. Hanhart, Medical Clinic, University Hospital, Zurich.

Professors Werner Jadassohn and Rolf Meier of Geneva and Basel, respectively, already belong to the International Association of Allergists.

In Holland the following have been elected:

Prof. P. Formijne, Head of the Medical Clinic, Wilhelmina University Hospital, Amsterdam.

Prof. Adrianus de Kleyn, Head of the Otological Clinic, Wilhelmina University Hospital, Amsterdam.

Prof. C. P. Prakken, Head of the Dermatological Clinic, "Binnen Gasthuis" University Hospital, Amsterdam.

Asst. Prof. H. A. E. van Dishoeck, Head of the Out-Patient Department for Allergic Diseases of the Otological Clinic, Wilhelmina University Hospital, Amsterdam.

Dr. C. Postma, M.D., Consulting Dermatologist, Wilhelmina University Hospital, Amsterdam.

Dr. W. Kremer, M.D., Head of the "Allergy Clinic of Amsterdam," Emmastraat 28, Amsterdam.

Dr. S. P. Klein, M.D., Associate of the "Allergy Clinic," Emmastraat 28, Amsterdam.

Dr. J. Bartels, Otological Clinic, Wilhelmina University Hospital, Amsterdam.

Dr. H. C. Olislagers, Medical Clinic, Wilhelmina University Hospital, Amsterdam.

Plans are now being made with S. Karger, medical publishers of Basel and New York, to publish an *International Archives of Allergy*, which will be the official journal of the International Association of Allergists. The Editorial Board will consist of internationally known scientists representing the various specialties of medicine to which allergy and immunology are applied. The publication will be quarterly and the articles may be published in the respective language of each country.

#### ASTHMA THROUGH THE AGES

This was the name given to a most interesting exhibit shown at the recent meeting of the American Medical Association. It was prepared by one of the past presidents of the College, Dr. Leon Unger, and his associates, Herman A. Levy, Albert H. Unger, and Isabelle Brandt Eisele of Northwestern University Medical School and Wesley Memorial Hospital, Chicago.

## NEWS ITEMS

Murals which illustrated the highlights in the history of the study of asthma were exhibited. One scene was from the ancient and medieval period to 1500 A.D.; one from the preindustrial period (1500-1900 A.D.); and two from the modern and contemporary periods since (1900 A.D.). Portraits of twenty men who were pioneers in the study of asthma, with a list of contributions of each, were also shown. The exhibit demonstrated present views regarding etiology, pathology, diagnosis, prevention and treatment of bronchial asthma. The education of the physician and the public was stressed. The display included preserved emphysematous lungs, and chest x-ray films of asthma and its complication. Reprints and information leaflets which deal with etiology, diagnosis, differential diagnosis, treatment and results of treatment were distributed.

This exhibit will be shown for three months at the Dallas Texas Health Museum and will also be a part of the October meeting of the Wisconsin State Medical Society in Milwaukee.

The exhibitors are to be congratulated, for contributions of this type do much to educate both the medical profession and the public to the importance of allergy.

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### FALL INSTRUCTIONAL COURSE GRANTS

The College gratefully acknowledges the following contributions for scholarships at \$100 a registrant for the Fall Instructional Course in Allergy held at the University of Cincinnati Medical School, Cincinnati, Ohio, November 3-8, 1947:

Anonymous .....	\$500
Marcelle Hypo-Allergenic Cosmetics, Chicago, Illinois.....	300
Almay, Inc., New York, New York.....	200
E. A. Brown.....	100

The Scholarship Committee awarded the scholarships to the following men: John Argabright, Fred D. Droege, Benigno Garat, W. R. Katzenmeyer, Joseph Kessler, Jacques Leger, Harry C. Shirkey, A. B. Vicencio, A. S. Weiland, Jacques Schlafer.

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### SOUTHERN SWEDISH ALLERGY FORUM

The Southern Swedish Allergy Forum, which exists in close contact with the University of Lund, joined the International Association of Allergists last August. The Board of Regents are: Prof. Goesta Dohlman, head of the Otolaryngological Clinic of the University of Lund, chairman; Dr. Hjalmar Koch, assistant in the Department of Otolaryngology, University Hospital (Lund), secretary, and Dr. Paul Kallós, F.A.C.A. (Hon.), Helsingborg, Sweden, member Executive Committee, International Association of Allergists, Editor of "Progress in the Science of Allergy." Professor Dohlman is a member of the Board of Regents of the International Association.

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We take pleasure in announcing the appearance of the new journal *Alergia*. This is published every four months, Volume 1, Number 1 covering the months of March through June. The publication is intended principally for those who are not allergists and is a synthesis of clinical and laboratory investigations in the field of allergy in the Argentine. The directors are: Doctors Guido Ruiz Moreno, Jose F. Dumm, Miguel A. Solari, Vicente Galvagno and Caupolicán Castilla, all of Argentina. The subscription price outside the Argentine is eight pesos and may be obtained by writing to Maria C. Aznarez De Lothringer, Anchorena 1338—3er. piso, Dpto. B—Buenos Aires.

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Publication of Fortschritte der Allergielehre Vol. II on Progress in the Science of Allergy has been announced. This volume is edited by Dr. Paul Kallós of



## NEWS ITEMS

Helsingborg, Sweden, and published by S. Karger, medical publishers of Basel and New York. The following are the contributors: Harold A. Abramson, New York; Karl Bucher, Basel; Robert A. Cooke, New York; Liselotte Deffner-Kallós, Helsingborg; French K. Hansel, St. Louis; Holger Haxthausen, Copenhagen; Elvin A. Kabat, New York; Paul Kallós, Helsingborg; Foster Kennedy, New York; Hjalmar Koch, Lund; Rolf Meier, Basel; Frank Simon, Louisville; Lewis Stevenson, New York; Fred W. Wittich, Minneapolis.

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Hyman Miller, M.D., F.A.C.A., announces the association of Ben C. Eisenberg, M.D., in the practice of Allergy, 201 South Lasky Drive, Beverly Hills, California.

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M. Coleman Harris, M.D., F.A.C.A., 444 North Bedford Drive, Beverly Hills, California, has recently been promoted to Associate Clinical Professor of Medicine in the Department of Medicine (Allergy) at the College of Medical Evangelists, Los Angeles.

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Dr. Benigno Garat, Buenos Aires, Chief of the Section of Allergic Diseases and Director of the Institute of Allergic Diseases of the Argentine, a Fellow of the College and the International Association of Allergists, is visiting the leading allergy clinics in the United States and Canada. Dr. Garat spent a week at the headquarters of the College and the International Association in Minneapolis.

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Dr. Marion B. Sulzberger and Dr. Rudolf L. Baer announce that as of September 15, 1947, they are no longer associated in the private practice of dermatology. Doctor Sulzberger will continue his practice at 999 Fifth Avenue, New York 28, New York, and Doctor Baer will continue his practice at 962 Park Avenue, New York 28, New York.

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Dr. Harold H. Golz, formerly of Clarksburg, West Virginia, has been appointed medical consultant to the Arabian American Oil Company. His new address is: Dr. Harold H. Golz, c/o Arabian American Oil Company, Dhahran, Saudi Arabia.

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Warren F. Kahle, M.D., F.A.C.A., announces the removal of his office to Suite 720, Medical Arts Building, Houston, Texas. His practice is limited to Internal Medicine and Allergy.

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Arnold S. Greenberg, M.D., announces the opening of his offices at 1925 Eye Street, Northwest, Washington 6, D. C.

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George J. Seibold, M.D., announces reopening of offices at 1310 Ninth Street, Wichita Falls, Texas.

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Tell Nelson, M.D., former member of the Board of Regents, announces the opening of offices at King Kalakaua Building, 1415 Kalakaua Avenue, Honolulu, Hawaii. Practice limited to Allergy.

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Roy A. Ouer, M.D., announces the opening of new offices at 2405 Fourth Avenue (corner Kalmia), San Diego, California. Practice limited to Internal Medicine (diagnosis and allergy).

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# BOOK REVIEWS

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OFFICE IMMUNOLOGY. Including Allergy. A guide for the Practitioner. Edited by Marion B. Sulzberger and Rudolf L. Baer. 420 pages, 8 chapters, 26 tables, 16 illustrations. Price \$6.50. Chicago: Year Book Publishers, Inc., 1947.

This comprehensive general practice manual has as its authors six authorities in their respective fields of dermatology, dermatologic allergy, internal medicine, allergy, pediatrics and immunology.

There has been a real need for practical detailed procedures in clinical immunology and allergy to be assembled under one cover which this manual accomplishes. The first two chapters deal with the common techniques, diagnostic procedures, prophylactic and therapeutic measures. There are complete chapters on the immunology of infections and dermatologic immunology, the immunologic management of spider, insect and snake bites, the immunologic principles of Transfusion Reactions—the Rh Factor. Respiratory allergies and miscellaneous allergies are adequately treated in separate chapters. Particulars of history taking, skin tests of all types, their interpretation and valuation, materials, how prepared or where obtained, dosages, medications, contraindications, and elimination or avoidance measures are presented with such exact directions so that reactions and errors are reduced to a minimum.

The etiological factors in drug eruptions, eczematous contact-type of allergic dermatitis, atopic dermatoses, fungus infections and their allergic manifestations are discussed in full.

The paper is of good stock, the illustrations and print are very clear and the book is of the handy desk reference size.

No physician who is applying clinical immunologic or allergic procedures in his office can afford to be without this manual.

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THE 1947 YEAR BOOK OF DERMATOLOGY AND SYPHILOLOGY. By Marion B. Sulzberger, M.D., and Rudolf L. Baer, M.D. 638 pages, 13 articles, 84 figures. Price \$3.75. Chicago: The Year Book Publishers, 1946.

This compact review of the literature on the subject of dermatology and syphilology continues to be of its usual high standard. Selected articles are assembled representing advances in dermatologic management with appreciation of contraindications or the inadequacies of therapeutic procedures. The general principles of the use of the antibiotics, topical applications, vitamins and hormones are reviewed. Outstanding advances in the diagnosis and treatment of dermatologic and venereal diseases by an authoritative evaluation of the many contributions adds greatly to its value.

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THE 1946 YEAR BOOK OF THE EYE, EAR, NOSE AND THROAT. By Louis Rothman, M.D., Samuel J. Crowe, M.D., with the collaboration of Elmer W. Hagens, M.D. 543 pages, 103 figures. Price \$3.75. Chicago: The Year Book Publishers, 1946.

This year book becomes a distinct improvement over its predecessor with important additions which bring it up to date.

The book is divided into three parts: Part I deals with sixteen articles which embrace all the diseases involving the eye, Part II contains five articles on the ear and Part III four articles on the nose and throat.

In the section on nose and throat, the sinuses and allergic conditions are presented in considerable detail from the recent literature. With the vast accumulating literature on diseases of the eye, ear, nose and throat, and the restrictions placed upon such a review by the size and format of the book, the authors are to be congratulated on its inclusiveness.

## BOOK REVIEWS

**ALLERGY IN THEORY AND PRACTICE.** By Robert A. Cooke, M.D. 572 pages. 32 chapters. 43 illustrations. Price, \$8.00. Philadelphia and London: W. B. Saunders Co., 1947.

This book, written in association with thirteen collaborators, is a comprehensive compilation and mainly represents the postgraduate teaching of allergy in New York City of the author and his associates. There are nine sections and an appendix.

Section I, on the fundamental aspects of allergy, is exceptionally good and is presented in a very lucid manner. Allergy of the various domains of the body is covered by authorities as fully as the scope of the book permits. There is also a section of detailed technics. The opinions of the contributors are somewhat arbitrary when omitting the published views of other authorities which would make the text more complete and increase its value as a reference book. The illustrations are excellent. The book is particularly compact and valuable to the advanced student of allergy.

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**DIAGNOSIS AND TREATMENT OF DIARRHEAL DISEASES.** W. Z. Fradkin, M.D. Foreword by Burril B. Crohn, M.D., 264 pages, 114 illustrations. Price \$5.00. New York: Grune and Stratton, 1947.

The contents are divided into three parts. I. General Considerations. II. Specific Diarrheal Disease. III. Diarrheal Diseases of Infants and Children. The book is a short practical conservative presentation in all of its phases of this field of gastroenterology.

Diarrheas reached increasing importance during and since the war, and newer diagnostic and therapeutic measures were developed. The author adequately covers these clinical, roentgenologic and laboratory aspects in a simple, direct, and practical manner.

There are chapters, containing illustrations, on Allergic Diarrhea and Psychogenic Diarrhea. The illustrations of protozoa and intestinal worms causing diarrhea make their identification relatively simple. The book is a practical guide for both the general practitioner and the specialist. The publishers are to be congratulated on the quality of paper and clear illustrations.

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# ANNALS of ALLERGY

*Published by the  
American College of Allergists*

Volume 5

November-December, 1947

Number 6

## IMMUNITY TO DIPHTHERIA INDUCED BY A BOOSTER DOSE OF DIPHTHERIA TOXOID PURIFIED BY ABSORPTION AND ELUTION

*Based on a Study of Fifty-five Allergic Children*

M. MURRAY PESHKIN, M.D., F.A.C.A., and H. G. RAPAPORT, M.D., F.A.C.A.  
New York, N. Y.

DESPITE the numerous investigations conducted over a period of years to purify diphtheria toxin and toxoid, including experiments in absorption with calcium phosphate,<sup>1-7,11-13</sup> detoxified crude bacterial filtrates and alum-precipitated toxoids are still mainly used in prophylaxis against diphtheria. As a consequence, frequently disturbing undesirable systematic reactions occur, especially after the administration of a booster dose of toxoid to older children. It becomes obvious, therefore, to replace the toxoids used now with preparations capable of causing minimal undesirable local and systemic reactions.

Crude toxoid prepared by detoxification of bacterial filtrates with formalin, in addition to proteins of true exotoxin, contains somatic antigens, i.e., soluble substances of proteinic nature that form precipitins with antibacterial serum. The biological significance of these substances and methods of their separation from the toxin have been described fully by Parfentjev, Waldschmidt and Weil.<sup>9</sup> It was shown that under controlled conditions selective absorption of somatic antigens with magnesium hydroxide can be achieved. This absorption, however, resulted in very little reduction of the total nitrogen content in the toxin. In a later work, Parfentjev and Goodline<sup>8</sup> described the methods of purification of toxoid prepared from absorbed toxin. By these methods they were able to eliminate more than 90 per cent of the original nitrogen. Purified toxoid was prepared from absorbed toxin by the subsequent steps of detoxification with formaldehyde, dialysis, absorption of the

From the Children's Allergy Clinic, The Mount Sinai Hospital, New York.

Dr. I. A. Parfentjev, of the Lederle Laboratories, gave technical assistance in this study. The preparations of calcium phosphate diphtheria toxoid and eluted diphtheria toxoid used in this study were furnished by Lederle Laboratories, Pearl River, New York.

Presented at the third annual meeting of the American College of Allergists at Atlantic City, New Jersey, June, 1947.

NOVEMBER-DECEMBER, 1947

TABLE I. DIPHTHERIA ANTITOXIN TITERS OF FIFTY-FIVE ALLERGIC CHILDREN OBTAINED AFTER THE BOOSTER INJECTIONS OF CALCIUM PHOSPHATED OR ELUTED DIPHTHERIAL TOXOIDS

Antitoxin Titer, Units per c.c. of Serum Before and After Injection of Toxoid										
Case Number	Before Booster Dose	After Booster Dose of 1 C.C.			Case Number	Before Booster Dose	After Booster Dose of 0.5 C.C.			
		Week	Months				Week	Months		
			1	2				1	2	
Calcium Phosphated Diphtherial Toxoid										
1.	>0.02	<0.04	0.1	>0.02	<0.04	19.	0.1	0.2	2.0	2.0
2.	0.2	<0.1	4.0	>3.0	<6.0	20.	0.1	1.0	>0.2	<0.5
3.	>0.2	<0.5	2.0	>2.0	<4.0	21.	0.1	>2.0	>2.0	<4.0
4.	>0.2	<0.5	6.0	10.0	16.0	22.	>0.1	6.0	6.0	6.0
5.	>0.2	<0.5	>6.0	<12.0	12.0	23.	0.2	4.0	>4.0	<8.0
6.	>0.2	<0.5	12.0	12.0	>12.0	24.	>0.2	2.0	>4.0	<8.0
7.	>0.2	<0.5	14.0	<24.0	3.0	25.	>0.5	2.0	>5.0	<14.0
8.	>0.5	<1.0	4.0	10.0	10.0	26.	0.5	>6.0	>5.0	<10.0
9.	>0.5	<1.0	>5.0	<10.0	10.0	27.	0.5	8.0	>10.0	<20.0
10.	>0.5	<1.0	12.0	20.0	20.0	28.	0.5	12.0	>8.0	<8.0
11.	>0.5	<1.0	10.0	10.0	10.0	29.	1.0	4.0	>6.0	<6.0
12.	>30.0	<60.0	>30.0	<8.0	30.0	30.	1.0	4.0	>12.0	<15.0
13.	>8.0	<16.0	8.0	>4.0	<8.0	31.	1.0	6.0	>6.0	<6.0
14.	>1.0	<2.0	6.0	12.0	16.0	32.	>1.0	4.0	>6.0	<12.0
15.	>1.0	<2.0	>8.0	<16.0	20.0	33.	>1.0	>6.0	>3.0	<6.0
16.	>1.0	<2.0	20.0	20.0	14.0	34.	2.0	4.0	>3.0	<6.0
17.	2.0	<4.0	12.0	14.0	20.0	35.	2.0	8.0	>3.0	<6.0
18.	4.0	<6.0	>10.0	<20.0	20.0	36.	>3.0	>4.0	>3.0	<6.0
Eluted Diphtherial Toxoid										
37.	0.002	>8.0	0.02	>8.0	<16.0	46.	0.01	0.2	>2.0	<4.0
38.	>0.1	<0.5	>4.0	<6.0	8.0	47.	>0.01	2.0	8.0	14.0
39.	>0.5	<1.0	>8.0	<16.0	20.0	48.	>0.01	4.0	4.0	<16.0
40.	>0.5	<1.0	>30.0	<60.0	>30.0	49.	>0.1	>0.5	1.0	>8.0
41.	1.0	<4.0	6.0	12.0	16.0	50.	>0.1	>0.5	>4.0	<12.0
42.	1.0	<4.0	16.0	15.0	15.0	51.	>0.1	>0.5	>4.0	<12.0
43.	>8.0	<16.0	16.0	>10.0	<20.0	52.	>0.5	8.0	>32.0	<100.0
44.	>16.0	<32.0	>15.0	>15.0	<30.0	53.	>0.5	20.0	>8.0	<16.0
45.	2.0	<4.0	>15.0	<30.0	20.0	54.	>2.0	>10.0	>16.0	<32.0
						55.	>4.0	>20.0	>20.0	<40.0

toxoid with calcium phosphate, and finally, elution of the purified toxoid. This method yields a highly purified product which contained very little nitrogen (250 Lf per c.c.), was free from bacillary proteins, and remained highly antigenic. Injections of this purified diphtherial toxoid into animals has shown its antigenic properties to be unimpaired.

In this communication fifty-five allergic children with bronchial asthma or hay fever or both were selected for injection with these purified diphtherial toxoids. All of these children had been previously immunized with combined diphtheria and tetanus toxoids, alum-precipitated<sup>10</sup>. Their average age was fourteen and one half years. The purpose of this investigation was to determine (1) the incidence of local and systemic reactions in allergic children following a booster dose of highly purified diphtherial toxoids in an age group of children in whom unfavorable reactions following a booster dose of crude diphtherial toxoid occurs most frequently, (2) the time of maximum antitoxin response, and (3) the incidence of positive cutaneous tests to the purified and crude diphtherial toxoids.

#### MATERIALS AND METHODS

The total number of samples of blood titrated for diphtheria antitoxin from the thirty-six allergic children injected with the booster dose of calcium phosphated toxoid was 143. The total number of titrations from nineteen allergic children given the booster injection of eluted diphtheria toxoid was seventy-one. A grand total of 214 samples of blood had been titrated after the booster injections. The dose consisted of 0.5 c.c. or 1 c.c. of the calcium phosphated toxoid or the eluted toxoid, injected subcutaneously.

#### TIME OF OCCURRENCE OF MAXIMUM RESPONSE TO THE TOXOID PREPARATIONS

A review of Table I shows the calcium phosphated and eluted diphtherial toxoids to possess marked antigenic potency, a booster dose of either toxoid causing the levels to rise as high as 40 units of antitoxin per cubic centimeter of blood. Moreover, there is no appreciable difference in the antitoxin response after a booster injection of 0.5 c.c. or 1 c.c. of either toxoid preparation. For this reason there will be no segregation of the maximum antitoxin values obtained.

To determine the maximum antitoxin response following a booster toxoid, two or more tests were done on fifty-five patients within two months after the injection. The maximum antitoxin response occurred after one week in ten children, after one month in twenty children, and after two months in twenty-five children.

#### REACTIONS AND SENSITIVITY

*Calcium phosphated toxoids.*—Fourteen children subcutaneously injected with 1 c.c. of the toxoid were available for study. Seven children

had severe, hot and painful local reactions lasting up to four days. In four of these seven children the swelling was about the size of a small orange, and in the other three children the swelling involved the entire arm. On the seventh day the swelling became moderate and indurated, which progressively grew smaller and by the sixteenth day was about gone. Three of these children had an elevation of temperature up to 101.5° F. lasting one day. One of these patients also had a severe headache.

Five patients had only a moderate local reaction for from one to four days with some pain at the site of the reaction.

One patient had only a slight local reaction and another patient had none.

Another group of sixteen children injected with 0.5 c.c. of the calcium phosphated toxoid were available for study. Nine children had a severe local reaction lasting for three days. The induration cleared in two weeks. In one of the nine children the swelling involved the entire arm. Two of these nine children had an elevation of temperature to 100.8° F. for one day, and a third child had a temperature of 102° F. for two days with urticaria. The latter child had been previously cleared of hives which was caused by contact with wool.

Six children had moderate local reactions and two of these children also had malaise and anorexia for one day after the injection of toxoid. The reactions were painful for several days in three of these six children.

The remaining patient had only a slight local reaction.

*Calcium phosphated and eluted toxoid.*—Six patients injected with 1 c.c. of the toxoid were available for report. Three of these patients had severe local reactions for three days with malaise and anorexia for one day.

Two patients had moderate local reactions for a few days and another patient had no local reaction.

None of the patients in this group had an elevation of temperature following the injection of the toxoid.

Another group of seven patients injected with 0.5 c.c. of eluted toxoid were available for study. Only one patient had a severe local reaction, the swelling involving the entire arm for five days. He also had a temperature up to 104° F. for three days. Chills started twelve hours after the injection.

Two patients had a moderate local reaction, another one a slight local reaction, and the remaining three patients had no local reaction. None of the patients in this group had an elevation of temperature after the injection.

Despite the elimination of over 90 per cent of the nitrogen in the preparations employed, the occurrence of severe local reactions following a booster dose associated with elevation of temperature occurred

frequently enough with the calcium phosphated toxoid to preclude its use in the immunization of children against diphtheria. The eluted calcium phosphated toxoid may be employed for immunization since the incidence of reactions following booster doses, especially the febrile type in older children, is less than that experienced by another comparable group of children injected with combined diphtheria and tetanus toxoids, alum-precipitated.<sup>10</sup>

Comparative intradermal tests with 1 to 100 dilution of crude yellow diphtherial toxoid and eluted calcium phosphated toxoid in 113 allergic children from eight to fifteen years of age (all of whom had received immunization against diphtheria in early childhood and many of whom had had subsequent booster doses) showed positive delayed reactions with the yellow toxoid in twelve children, four of whom also reacted positively to the eluted toxoid. Another ten children reacted to both the crude and eluted toxoids but the reactions to the eluted toxoids were definitely smaller than those with the yellow toxoid. No child who was negative to the eluted toxoid reacted positively to the yellow toxoid.

From this it appears that despite the technical advantages of the eluted toxoids over the crude yellow toxoid, children still react by the test to the eluted preparation, though much less frequently and less intensely than with the yellow toxoid.

In view of the above findings, the eluted calcium phosphated toxoid can be regarded as a preparation pointing to definite progress in the search for a diphtherial toxoid capable of lowering the incidence of local febrile or systemic allergic reactions following its use.

#### SUMMARY

1. Fifty-five allergic children with bronchial asthma or hay fever or both were injected with purified diphtherial toxoids. Calcium phosphated toxoid was prepared from absorbed toxin by the subsequent steps of detoxification with formaldehyde, dialysis, absorption of the toxoid with calcium phosphate, and eluted toxoid was prepared by the elution of the purified calcium phosphated toxoid.

2. These purified diphtherial toxoids equally possess marked antigenic potency. There was no appreciable difference in the antitoxin response after an injection of 0.5 c.c. or 1 c.c. of either toxoid preparation.

3. The maximum antitoxin response for the majority of children with each toxoid preparation occurred from one to two months after injection.

4. Despite the elimination of over 90 per cent of the nitrogen in the preparations employed, severe local and systemic reactions occurred sufficiently often following the injection of the calcium phosphated toxoid to preclude its use in the immunization of children against diphtheria. However, the eluted calcium phosphated toxoid may be employed for immunization with advantage, since the incidence of reactions following injections, especially the febrile type in older children, is less than that



experienced by another comparable group of children injected with alum-precipitated toxoid.

5. Comparative intradermal tests with 1:100 dilution of crude yellow diphtherial toxoid and eluted calcium phosphated toxoid showed the latter preparation to give a decidedly lower incidence of positive reactions.

6. The eluted calcium phosphated diphtherial toxoid can be regarded as a preparation pointing to definite progress in the search for diphtherial toxoid capable of lowering the incidence of local, febrile or systemic allergic reactions following its use in allergic children.

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All periodical publications of the British Medical Association are now obtainable through Grune & Stratton, Medical Publishers, 381 Fourth Avenue, New York 16, New York, who have been appointed by the Association sole agents for the United States beginning with January, 1948.

The journals are: *British Medical Journal*, published weekly, \$14 a year; *Abstracts of World Medicine*, published monthly, \$13 a year; *Abstracts of World Surgery, Obstetrics and Gynecology*, published monthly, \$9 a year.

Quarterly journals obtainable at the uniform subscription rate of \$5.50 a year are: *Annals of the Rheumatic Diseases*, *Archives of Disease in Childhood*, *British Heart Journal*, *British Journal of Industrial Medicine*, *British Journal of Pharmacology and Chemotherapy*, *British Journal of Social Medicine*, *British Journal of Venereal Diseases*, *Journal of Clinical Pathology*, *Journal of Neurology, Neurosurgery and Psychiatry*, and *Thorax*.

# BRONCHIAL ASTHMA IN PATIENTS OVER THE AGE OF FIFTY-FIVE YEARS

## Diagnosis and Treatment

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BRONCHIAL asthma occurring after the age of fifty-five years is, in our experience, usually due with about equal frequency to food and inhalant allergy, rarely to drug allergy, and very rarely to bacterial allergy. This opinion is based on the demonstrated causes in 173 private patients who obtained excellent or good results from our treatment. To judge the results of our present therapy, only those patients seen during the last six years who co-operated for at least six months are considered. During this period 1,061 other private patients with ages from one to fifty-five years, suffering with bronchial asthma from similar causes, have obtained such results.

TABLE I. OCCURRENCE AND DURATION OF BRONCHIAL ASTHMA IN  
173 PATIENTS OVER THE AGE OF FIFTY-FIVE YEARS  
Successfully treated from 1940 to 1946

Males .....	98; Females .....	75
Onset of Asthma after 55 years.....	51 patients	
Onset of Asthma between 50 and 55 years.....	21 patients	
Duration of Bronchial Asthma		
0—1 year.....	22 patients	
1—2 years.....	22 patients	
2—5 years.....	39 patients	
5—10 years.....	36 patients	
10—20 years.....	16 patients	
Over 20 years.....	38 patients	
Perennial Asthma .....	129 patients	
Recurrent Exaggerations or Attacks.....	80 patients	
Seasonal Exaggeration:		
In Summer .....	30 patients	
In Fall .....	42 patients	
In Winter .....	55 patients	
In Spring .....	47 patients	

The number of males and females, the duration of the asthma, the frequency of perennial asthma, of recurrent attacks, and seasonal exaggeration of the symptoms are shown in Table I. Exaggeration in the fall, winter and spring months suggested that indoor inhalants and especially food allergy<sup>9</sup> might be responsible.

The frequency of other manifestations of allergy, especially perennial and seasonal nasal allergy, is shown in Table II. A history suggestive but not necessarily diagnostic of food allergy occurred in seventy-eight of the 173 patients. Such a history suggests but does not necessarily indicate clinical food allergy. The familiar predisposition to bronchial asthma in contrast to other manifestations of allergy is shown in Table III.

# BRONCHIAL ASTHMA—ROWE AND ROWE

## DETERMINATION OF THE ALLERGENIC CAUSES

*History.*—A detailed, well-taken history often indicates probable food, pollen or other inhalant allergies and justifies treatment based on such conclusions.

TABLE II. OTHER MANIFESTATIONS OF ALLERGY

Perennial Nasal Allergy .....	97 patients
Seasonal Nasal Allergy .....	33 patients
(In the Spring, Summer and Fall)	
Urticaria .....	15 patients
Eczema .....	17 patients
Gastrointestinal Symptoms .....	41 patients
Recurrent Headaches .....	24 patients
Dietary History—Positive .....	78 patients
Drug History—Positive .....	14 patients
Environmental History—Positive .....	39 patients

TABLE III. FAMILY HISTORY OF CLINICAL ALLERGY

Bronchial Asthma .....	81 patients
Nasal Allergy .....	18 patients
Recurrent Headaches .....	15 patients
Gastrointestinal Symptoms .....	6 patients
Urticaria .....	2 patients
Eczema .....	5 patients

The writers' plan for history taking is published elsewhere.<sup>5,6,7</sup> A dietary history is most important, based on questions about single foods, such as "Do you drink and like milk?", "Do you eat and like eggs?", et cetera. The drug history should include all reactions to drugs or medicaments. The environmental history should record all home, occupational and recreational sources of inhalants which might cause asthma.

*Skin Testing.*—The results of skin testing of these 173 patients in Table IV showed that reactions of varying degrees occurred in these elderly patients as in younger groups.<sup>11</sup> Skin testing was done by the scratch method. Intradermal testing with inhalant allergens which failed to react by the scratch method was also done in selected patients. Positive skin reactions usually occurred to inhalants and infrequently to foods responsible for the asthma. Positive reactions, moreover, were not always associated with clinical allergy, especially to causative foods.<sup>8,14</sup>

No skin reactions occurred in seventy-three of the 173 patients. Of these seventy-three patients, fifty-eight were allergic only to foods, eleven to pollens and foods and four to pollens alone. Thus, the fallibility of the skin test in the determination of food allergy and, to a lesser extent, inhalant allergy is demonstrated.

Because of the writers' experience that many intradermal tests with foods are not specific or indicative of past or potential allergy,<sup>8</sup> such testing is not routine.

*The Study and Control of Food Allergy.*—Because of this fallibility of the skin test in the determination of food allergy, we have used the senior

# BRONCHIAL ASTHMA—ROWE AND ROWE

TABLE IV. NUMBER OF PATIENTS WHO REACTED TO INDIVIDUAL ALLERGENS IN VARIOUS GROUPS BY THE SCRATCH TEST

Degree of Reaction	0 — 1+	2 — 5+	6 — 10+	Total Patients
Grass	22	33	7	62
Fall	17	23	13	53
Tree	23	22	5	50
Flowers	15	28	2	45
Animal Emanations	13	26	1	40
Miscellaneous Inhalants	24	15	1	40
House Dust	19	20	0	39
Fungi	8	10	0	18
Food	13	17	1	31

Seventy-three patients gave no skin reactions to any food or inhalant allergens.

writer's elimination diets<sup>7</sup> to study suspected food sensitization. For fifteen years the cereal-free elimination diet has been preferred because of the frequency of allergy to the cereal grains (one or more) as well as to milk, egg, wheat, chocolate and other foods excluded from the diet. These diets are modified when there is evidence of allergy to included foods.

The advantages of the standardized elimination diets are that the patient is given (1) a specific list of allowed foods, (2) detailed menus, (3) specified amounts of foods which will maintain or increase weight, (4) tested recipes for bakery products, (5) proper amounts of calcium and specified vitamins, and (6) directions for eating away from home to prevent errors in the diet.

Good results require (1) absolute adherence to the diet, (2) frequent conferences with the doctor who must detect errors, either willful or unintentional, and (3) realization that relief will appear in two to fourteen days, depending on the time the allergens of formerly eaten foods remain in the body and the time required for the cells of the lungs to recover from the allergenic reactions.

The prolonged use of the elimination diets in these patients caused a gain of weight in sixty, no change in sixty-seven, desired loss of weight in twenty and undesired loss, moderate in degree, in only ten patients.

*The Study and Control of Inhalant Energy.*—Properly taken histories often indicate pollen, animal emanation, dust, fungus or other inhalant allergy. Skin tests to the causative inhalants at times are negative, though much less often than to allergenic foods. Positive reactions, moreover, may not be associated with clinical allergy.

Environmental control and pollen filters when indicated are beneficial. Desensitization usually is necessary to all suspected inhalants impossible to exclude from the patient's environment. This treatment usually requires successively stronger dilutions up to the 1:500 or the 1:50 dilution for satisfactory results. Co-seasonal therapy, however, requires very weak dilutions, such as a 1:5,000,000 or 1:5,000,000,000 or weaker.

## BRONCHIAL ASTHMA—ROWE AND ROWE

Prolonged desensitization for months or for one or more years usually is necessary.

Allergy to fungi is not common in California and the Southwest.

TABLE V. CAUSES OF BRONCHIAL ASTHMA DETERMINED BY GOOD RESULTS FROM SPECIFIC CONTROL

Food and Other Allergies .....	142 patients
Food Allergy Alone .....	70 patients
Inhalant and Other Allergies .....	114 patients
Inhalant Allergies Alone (Other than Pollen).....	15 patients
Pollen and Other Allergies .....	98 patients
Pollen Allergies Alone .....	16 patients
Animal Emanations and Other Allergies.....	24 patients
Miscellaneous Inhalant and Other Allergies.....	28 patients
House Dust and Other Allergies .....	35 patients
Fungus and Other Allergies.....	? patients
Bacterial and Other Allergies.....	5 patients

*Bacterial Allergy.*—In this series bacterial allergy was a major cause in no patient. It was of probable secondary importance to food and/or inhalant allergies in five patients. The fact that our good and excellent results were obtained in these 173 patients with no operations on the nose or sinuses except for the removal of polyps in three speaks especially against bacterial allergy as a cause. The writers agree with Rackeman,<sup>3</sup> Tuft<sup>13</sup> and others that hyperplasia, polyps and other changes in the nose and sinuses are due to allergy and not infection. Severe vascular allergy did not occur in any patient.<sup>2,4</sup>

*Physical Examinations and Laboratory Studies.*—Routine physical, blood and urine examinations, Kline tests and roentgen ray studies of the lungs and, when indicated, of the sinuses were made on all patients. The many, non-allergic causes of wheezing, cough and dyspnea, especially cardiovascular disease, were always in mind.

### CAUSES OF BRONCHIAL ASTHMA IN 173 PATIENTS OVER THE AGE OF FIFTY-FIVE YEARS WITH GOOD OR EXCELLENT RESULTS

To obtain these results, the allergies indicated in Table V were controlled. Excellent results mean complete freedom from symptoms or only slight occasional wheezing or coughing, except with failure to adhere to the necessary diet, environmental control or desensitization therapy. Good results mean relief from symptoms, except for occasional wheezing or coughing with exertion or at times during the night.

The frequency of food allergy as the sole cause and especially in association with inhalant allergies is shown in the table. Inhalants alone were responsible about half as often as were foods. In association with foods, they caused asthma a little less frequently than did foods in association with inhalants. The frequency of pollens, animal emanations and other inhalants is shown in the table.

## BRONCHIAL ASTHMA—ROWE AND ROWE

*Patients of Over Fifty-five years Who Were Unrelieved of Bronchial Asthma.*—During this six-year period, sixty-two additional patients over fifty-five years were seen. As shown in Table VI, co-operation was satisfactory in only seven and in four of these the period of co-operation was less than six months. Death occurred in one patient from spontaneous pneumothorax in eighteen hours after treatment was started.

TABLE VI. UNRELIEVED BRONCHIAL ASTHMA IN SIXTY-TWO PATIENTS OVER FIFTY-FIVE YEARS OF AGE SEEN SINCE 1940

Good Co-operation .....	7 patients
Poor Co-operation .....	55 patients
<i>Time of Treatment:</i>	
None .....	25 patients
1 to 4 weeks .....	17 patients
1 to 3 months .....	13 patients
3 to 6 months .....	4 patients
6 to 12 months .....	3 patients

### TREATMENT OF BRONCHIAL ASTHMA

#### *Specific Control.*—

1. When seasonal pollen, specific inhalant or drug allergies are not the sole obvious causes, food allergy is studied immediately with the senior writer's standardized cereal-free elimination diet.<sup>7</sup>

2. When inhalant allergy is indicated by history or skin testing, strict environmental control and, when necessary, desensitization with all allergens the patient continues to inhale are necessary.

3. Rare bacterial allergy, especially in teeth and less often in other foci, requires removal of such foci and, at times, careful desensitization with autogenous vaccine.

4. Allergy to drugs, especially to aspirin, must be remembered.

*Symptomatic Control.*—This is necessary until the above specific measures reduce or eliminate the symptoms.

1. Ephedrine by mouth with or without small doses of barbitol.

2. Aminophyllin, 3 to 6 grains by mouth, every six hours if necessary.

3. Potassium or sodium iodide, 5 to 20 drops of the saturated solution in water, two to four times a day. Allergy to iodine is indicated by swelling of the submaxillary glands, coryza, or nasal blocking, headaches or skin eruption.

4. Pyribenzamine or Benadryl by mouth.

5. Epinephrine 1:100 by inhalation.

6. Epinephrine 1:1000 subcutaneously, 0.3 c.c. to 0.8 c.c. every two hours if required.

7. Epinephrine in gelatin intramuscularly for a more prolonged effect.<sup>12</sup>

8. Aminophyllin, 3.5 to 7.5 grains by vein during a three- to five-minute period every eight hours if necessary for severe symptoms.

9. Morphine or other opiates, demerol, paraldehyde, chloral or barbitals are absolutely contraindicated, in our experience. Depression of the

respiratory center may lead to anoxemia and, at times, death. Atropin also is contraindicated.

10. When symptoms persist, roentgen ray therapy of the lungs or fever therapy may be tried with questionable benefit. Anesthesia, especially with ether in oil, is no longer advised. Bronchoscopy is only justifiable when bronchial obstruction from foreign bodies, tumors or large plugs of mucus is probable.

11. Antibiotic drugs are indicated for complicating infections of the lungs or other tissues.

12. Though reassurance has been routine, prolonged psychotherapy has not been used in any patient.

#### TREATMENT OF INTRACTABLE BRONCHIAL ASTHMA

##### *Specific Control.*—

1. These patients require hospitalization or comparable care at home. Immediate consideration of possible food, inhalant or rare bacterial allergy is imperative. Unless inhalants are the obvious sole cause, food allergy immediately is studied with the cereal-free elimination diet. Vomiting requires intravenous glucose in saline or water, according to fluid and salt requirements. Severe asthma may necessitate the elimination diet in liquid, soft, minced or pureed form, containing adequate calories. If food allergy is the cause, improvement may not be obvious for five to fourteen days. With improvement, the regular published menus should be used.

2. Inhalant allergy requires strict environmental control. Pillows and mattresses must be encased in dustproof covers. If pollen is suspected, a window filter is advisable. Desensitization should be started only after definite improvement occurs.

3. Bacterial and drug allergies need study as advised in moderate bronchial asthma.

##### *Symptomatic Control.*—

1. Epinephrine 1:1000 subcutaneously in doses of 0.5 c.c. to 0.85 c.c. every two hours may give relief.

2. If epinephrine is not effective, aminophyllin by vein in 5 to 7.5 grain doses every eight hours is indicated.

3. With dehydration, intravenous 5 per cent glucose in saline and water should be given.

4. For extreme dyspnea and especially cyanosis, oxygen by a BLB mask or tent is necessary.

5. As in moderate bronchial asthma, all sedatives are contraindicated.

6. With relief, measures for the control of moderate bronchial asthma described above will be effective.

#### CASE REPORTS

*Case 1.*—A woman, Mrs. C. P., aged sixty-six, was first seen on October 3, 1941, because of bronchial asthma since 1937. It started in December with moderate symp-

toms. Wheezing and coughing continued, and in the late spring she went to New Mexico and Colorado, where relief occurred. Desensitization to molds was given. She returned to Indiana in September, and in October "when the furnaces were started," asthma returned and continued until early summer. Asthma returned in October and continued in spite of treatment. Being advised to move to an area free of smoke and dust in the winters, she came to Berkeley in 1940. Since then asthma has been absent, or very mild in the summers, returning in early October and continuing until the spring last year and being severe in the last three weeks.

She gave no history of any other manifestations of allergy. A "winter cough" had been present for five years before her asthma developed.

She knew that milk had caused asthma for three years, and she suspected meat, fish, various vegetables, citrus fruits and watermelon. Aspirin caused itching of the hands and feet, and quinine caused nervousness. Smoke and dust were suspected as causes of the asthma.

Her maternal uncle had bronchial asthma.

Her physical examination was negative except for diffuse evidences of bronchial asthma in her lungs. Her blood pressure was 150/90. Her blood and urine analyses were normal. The roentgen-ray of her lungs showed moderate emphysema.

Skin testing with all important foods gave no reactions. Skin testing with all important inhalants gave 1-plus and 2-plus reactions to several fall pollens and goose feathers.

*Treatment and Progress.*—She was placed on the writer's cereal-free elimination diet and given 12 drops of saturated solution of potassium iodide three times daily. In three days, she reported great relief and undisturbed sleep. In two weeks, she was so well she motored by way of the Southwest to Indiana to her son's wedding, returning to Berkeley in December. In Indiana she remained on her elimination diet all the time. No asthma occurred even though the furnaces were on, and she slept in bedrooms in which environmental control was absent.

Since then no asthma has occurred except when she has taken milk, egg, fish or wheat from September to May. In the summer months if moderate amounts of these foods are eaten, slight occasional asthma occurs.

*Comment.*—Food allergy was the sole cause of this patient's bronchial asthma which first developed at the age of sixty-two years. The winter cough for five previous years probably was the equivalent of the asthma. No previous clinical allergy had occurred in her life.

The negative skin reactions to the allergenic foods, and the absence of clinical allergy to the inhalants which gave positive reactions, illustrate the fallibility of the skin test in determining the causes of clinical allergy.

The activation of her bronchial asthma in October in Indiana, continuing through the winter to late spring, had been ascribed to "smoke from furnaces and dusts." The same activation, however, continued for two years in Berkeley where no coal or other smoke is in the air. The entire control of her asthma from fall to late spring for the last five years with the elimination diet shows that the activation of the asthma was due to the decreased tolerance for allergenic foods during the fall to late spring, which one of the writers has long reported in certain patients.<sup>9</sup> The absence of asthma in Indiana in December after being on the elimination diet for only one month, being in the same house where asthma had been severe in former Decembers, stresses the important role of food allergy in the production of her asthma.

*Case 2.*—A man, Mr. H. G., aged sixty-six, was first seen because of bronchial asthma in May, 1941. Coryza, lacrimation and itching of the eyes had occurred



five years before when threshing sugar beet seeds. Since then, in the winter months, nasal symptoms with a productive cough and a tightness in the chest had occurred. In June, 1940, these symptoms increased in degree, but were relieved in July and August. In the fall and winter, asthma persisted from sunset to sunrise and increased symptoms required hospitalization in February, March and May.

He gave no history of previous nasal or bronchial allergy or of any other manifestation of allergy. His dietary history revealed no idiosyncracies or dislikes for any foods. He lived on a ranch, but had no symptoms from inhalation of any tree, grass, weed or alfalfa pollens or any animal emanations or feed or grain dusts, rusts or smuts in the air.

Asthma had occurred in the mother and two maternal uncles.

Appendectomy in 1902 and polypectomy in 1940 had been done. His physical examination was negative except for diffuse evidences of bronchial asthma in the lungs and a blood pressure of 160/90. X-ray of the lungs showed moderate emphysema. His blood and urine analyses were normal except for an 8 per cent eosinophilia.

Skin testing with all important food and inhalant allergens by the scratch test was negative. Intradermal tests with inhalants gave 1-plus and 2-plus reactions to several of the grass and weed pollens and to dog and horse hair, silk, orris root, cottonseed and house dust allergens.

*Treatment and Progress.*—He was placed on the senior writer's cereal-free elimination diet and given 15 drops of saturated solution of potassium iodide three times daily and 1:100 epinephrine solution for inhalation. In two weeks his asthma had diminished and in two more weeks no attacks had occurred. His weight had increased from 162 pounds to 188 pounds.

Moderate nasal allergy continued, but no dust or pollen therapy was given. In two months his symptoms had disappeared and he was doing light ranch work. No asthma recurred, and in the summer of 1943 a general diet was resumed. In November asthma recurred and persisted until the cereal-free diet was resumed in late December. Since then rice, corn, and rye have been taken in the summer, but the strict diet, plus turkey, ham and all vegetables and fruits, has been followed each fall and winter. No asthma has been present. His recent weight is 192 pounds.

*Comment.*—The development of bronchial and nasal allergy at the age of sixty-one years without any previous evidence of allergy shows that hypersensitivity can arise in old age. The control of his asthma with the elimination diet without desensitization to any pollen or other inhalant to which his history and skin reaction indicated probable clinical allergy is of interest. The necessity of eliminating the cereal grains in winters and his tolerance of these during the summers illustrates the exaggeration of food allergy during the winter. The rapid gain of weight shows that nutrition and weight can be maintained with the writer's elimination diet.

*Case 3.*—A woman, Mrs. J. P., aged sixty, was first seen in February, 1944, because of bronchial asthma present for thirty years. She had been in Vallejo, California, for one year, having lived previously in British Columbia and in Kansas. Her asthma had always occurred in August, September and October. For the last eight months in Vallejo on the bay, asthma had continued every day and night.

Hay fever had recurred from August until the frosts for thirty years. Sneezing from dusts and soap powders also had occurred.

Recurrent headaches had been present for thirty years up to twelve years ago. Much distention, belching and constipation had occurred for fifteen years.

Her dietary history revealed the production of distention and gas in the colon from milk. At times all foods seemed to disagree. Her drug and environmental histories were negative from the allergic viewpoint.

In the family, the mother had had sick headaches, and one brother and two sisters had asthma.

Her physical examination was negative except for rhonchi, wheezing and râles throughout both lungs. Roentgen-ray of the lungs revealed moderate emphysema with depressed diaphragms. Her blood and urine analyses and her Kline test were negative.

Skin testing by the scratch method with all important inhalants showed a 3-plus reaction to feathers, 1-plus and 2-plus reactions to most of the grass pollens, 2-plus to 8-plus reactions to cocklebur and most of the chenopod, artemesia and ambrosia pollens, 2-plus to 5-plus reactions to chrysanthemum, cosmos and dahlia pollens and 1-plus to 2-plus reactions to acacia, oak, walnut and olive pollens. She also gave 2-plus reactions to stock house dust extracts.

Skin testing by the scratch method with all important foods gave no positive reactions.

*Treatment and Results.*—The writer's cereal-free elimination diet was ordered for the study of possible food allergy. In two weeks the asthma present for eight previous months was practically absent, and only one pillow was used at night.

Pollen therapy then was initiated with a 1:500,000 dilution of a multiple spring, summer and fall antigen. Moderate increase in the asthma occurred during the following eight weeks. With the reductions of the dose to the 1:50,000,000 dilution and the maintenance of the original diet, the asthma practically disappeared. In the next month it was found that 0.3 c.c. of this weaker dilution reproduced moderate asthma whereas 0.1 c.c. controlled the symptoms.

During the last two years 0.1 c.c. subcutaneously of the 1:50,000,000 dilution of the pollen antigen has been given the patient two times a week, and the cereal-free elimination diet, plus fish, all vegetables and fruits, has been continued. During the summer months rice, corn and rye have been eaten, but during the late fall and winter they have been excluded because of a cough and wheezing which gradually developed with their use. With the above treatment she was even free of asthma in Kansas in March, and only slight tightness in the chest occurred for two weeks in the fall of 1945 and none in 1946.

*Comment.*—The history of hay fever and asthma from August to November for thirty years in Kansas and for one fall in California, together with the large reactions to all types of pollen, stresses pollen as a major cause. In Kansas no clinical manifestations occurred from the grass and tree pollens which gave the reactions.

The writers' results from pollen therapy illustrate the value of the very dilute multiple antigens for the control of pollen allergy in some patients. The relief of her symptoms with 0.1 c.c. and not 0.3 c.c. of the 1:50,000,000 dilution illustrates similar experience in other patients.

Her asthma, present for the first time in the winter, was relieved in two weeks after the cereal-free elimination diet was given and before pollen therapy was started. This indicated food allergy as a cause. Since then it has been determined that cereal grains can be eaten in the summer without resultant asthma. During the winter months asthma has recurred unless the cereals have been removed from the elimination diet. This illustrates the writers' observations that food allergy is activated in some patients in maritime areas and during the fall to spring months.<sup>10</sup>

## SUMMARY

1. Food and inhalant allergies with approximately equal frequency are the usual causes of bronchial asthma in patients over the age of fifty-five years, as they are in all other ages.

2. The recognition of the importance of food allergy has depended on the routine use of our standardized cereal-free elimination diet whenever food allergy was suspected. Clinical food allergy rarely could be demonstrated by skin testing.

3. The treatment of inhalant allergy has required strict environmental control when indicated and desensitization with inhalants which could not be excluded from the air of the patient's environment.

4. Though gradually increasing and final large doses of antigens usually were necessary for good results, some cases required extremely weak dilutions, especially during co-seasonal therapy.

5. The minimal evidence of infective asthma due to bacterial allergy and of unknown obscure intrinsic causes coincides with our experience in other ages.

6. The specific and symptomatic control of symptoms in moderate bronchial asthma and in intractable bronchial asthma is discussed.

7. Sedatives of all types are contraindicated since they depress respiration and at times result in death.

8. Antibiotics are required when a secondary bacterial infection is present.

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## THE ALLERGENS OF MILL DUST

### Asthma in Millers, Farmers, and Others

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AMONG all types of asthma which we consider to be occupational or connected with environment, asthma produced by inhalation of mill products, such as grains, dust, flour, and so on, has always been of special interest, as can be judged from the many papers published on this subject. The results are interesting because they explain asthma, not only in millers, but also in other workers who come in contact with the same products (laborers, bakers, and so forth) and even in people who have nothing to do with this work, since the allergens with which we are dealing, are conveyed by the air and can be of a more general importance, for example, the asthma epidemic described by Ancona,<sup>7</sup> due to the presence of *Tinea Granella* and *Pediculoides ventricosus* in the flour of a small village.

We have already published our own observations on this problem in successive papers,<sup>14-17</sup> and the aim of this article is to present a summary of our points of view.

It would be a mistake to uphold the concept that the cause of sensitization is always the same; the fact is, that in cereal or flour dust, and generally in the atmosphere of mills and factories and also in the air near by, in which a certain amount of dust from these establishments spreads, there can be found different elements, each of which can be the producer of sensitization in each case. This can be clearly seen when tests are made with intradermal injections using cereal extracts; in almost every person whose anamnesis would make us think of this sensitization, positive reactions can be seen; and in a high proportion of those cases with a positive intradermal reaction to cereal dust, passive transfer is positive with Prausnitz-Kustner's method. Some years ago, we gathered information in mills and factories and found that of 792 factory workers, thirty-six (4.5 per cent) had asthma and of 149 cases of millworkers, seventy-three (48.9 per cent) were asthmatic. Of all the cases of asthma which we were able to study well (fifty-two), a positive cereal-dust reaction was obtained in thirty-eight, and in 87.5 per cent of the tested cases (twenty-eight out of thirty-two), the Prausnitz-Kustner reaction was positive. The nature of the allergen, that for the time being remained obscure, was studied afterwards by us and other authors. We are now prepared to give the factors which can be taken as proven:

1. *Flour*.—Walker,<sup>28</sup> Grimm,<sup>8</sup> ourselves,<sup>15</sup> and others have shown the existence of real sensitization due to flour; in other papers,<sup>15</sup> we have

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NOVEMBER-DECEMBER, 1947

reported asthma cases with positive intradermal and Prausnitz-Kustner reactions. Therefore, no doubt whatsoever remains. Some authors have studied asthma or spastic coryza in bakers (De Bèsche, Salen, and Juhlin-Denfelt,<sup>22</sup> Van Dishoeck and Roux,<sup>25</sup> and so forth).

However, flour sensitization, often through the digestive route, is one of the most frequent allergens in cases of complex, airborne allergy, which manifests itself by leukopenia shock, by pulse frequency (Coca<sup>5</sup>), or by our method of microprecipitin reactions.<sup>1</sup> Although sensitization of this type can be shown in some cases, it occurs more frequently with vegetables. In Spain, sensitization to earob beans (*Vicia monantha*) in farmers, is relatively common, and we have shown, not only clinically with intradermal and Prausnitz-Kustner passive transfer reactions, but also by experimental investigations, that the sensitizing allergen is the vegetable flour itself, or its proteins. Female guinea-pigs were sensitized with concentrated dust absorbed on alumina, according to the method of Friedman, and shock produced with different dust fractions by means of the Schultz-Dale phenomenon. Thus, the pure flour of this vegetable more likely than not provoked shock. With the exception of bakers, however, sensitization to flour is extremely uncommon in the handling of cereals, as the cause of the bad effects of cereal dust.

2. *Infestation by acarina (mites).*—Beginning with Ancona's discovery,<sup>7</sup> previously mentioned, others have studied the part that similar infestations might play. S. Van Leuwen and collaborators<sup>26</sup> found that flours were frequently infested by a mite (*Tyroglyphus farinae*), which they believed was the cause of its selective allergic effects. Almost at the same time, we studied sensitization by mites and found others, as well as the *Alaerobius*, that in our country frequently infest granaries and corn warehouses as *Glyciphagus* and *Tyroglyphus*. This infestation, which can reach crevices in furniture and may become a real plague (Von Ludwig<sup>27</sup>) in living quarters, was also shown in some of our cases, and was observed by others as well (Dekker,<sup>9</sup> et al.). In some cases, and to a limited extent in the particular case of granary asthma, we have shown specific sensitization by extracts of acarina, but in no case were we able to show passive transfer with the Prausnitz-Kustner method, which is in agreement with Grove's observations of a case of asthma caused by *Pediculoides*. In some cases it is possible, even in the absence of the passive transfer, sensitization due to this mite, but we were soon able to see from our studies that dust infested by it also contains fungi, and we become more and more convinced that these are the ones which really sensitize, owing to the small size of the spores and their great diffusibility.

3. *Fungus infections.*—Cadham,<sup>3</sup> in 1924, showed sensitization by *Puccinia Granella* in workers in wheatfields, and this is the first observation

TABLE I

Name	Cereal reaction	Dust P-K	Tilletia reaction	Ustilago P-K	Pure reaction	Flour P-K
M. Rod. ....	pos.		pos.		neg.	neg.
C. Pasc. ....	pos.	pos.	pos.	pos.	neg.	neg.
V. Rod. ....	pos.		pos.	pos.	neg.	neg.
E. Torr. ....	pos.		pos.		neg.	neg.
J. Trev. ....	pos.		pos.	pos.	neg.	neg.
G. Mat. ....	pos.	pos.	pos.	pos.	neg.	neg.
P. Klor. ....			pos.	pos.	neg.	neg.
A. Garc. ....	pos.		pos.		neg.	neg.
P. Sanch. ....	pos.	pos.	pos.	pos.	neg.	neg.
B. Muin. ....	pos.		pos.		neg.	neg.
D. Mat. ....	pos.	pos.	pos.	pos.	neg.	neg.
L. Mart. ....	pos.	pos.	pos.	pos.	neg.	neg.
J. F. Es. ....	pos.		neg.		neg.	neg.
E. Rub. ....	pos.	pos.	neg.	neg.	neg.	neg.
A. F. Vaz. ....	pos.	pos.	pos.	pos.	neg.	neg.
M. Ahij. ....	pos.	pos.	neg.		neg.	neg.
J. J. Pr. ....	pos.	pos.	neg.		neg.	neg.
M. P. R. ....	pos.	pos.	pos.	pos.	neg.	neg.
F. Ast. ....	pos.	pos.	neg.		neg.	neg.
G. Barr. ....	pos.		neg.		neg.	neg.
A. Font. ....	pos.	pos.	neg.		neg.	
T. Ben. ....	pos.	pos.	neg.		neg.	
S. Serr. ....	weak	neg.	neg.		pos.	pos.
F. Mant. ....	weak	neg.	neg.		pos.	pos.

on the allergic value of fungi. Some time afterwards, S. Van Leuwen,<sup>26</sup> Hansen,<sup>10</sup> and ourselves,<sup>18</sup> were able to demonstrate sensitization by other fungi that eventually could be cultured from flours (*Aspergillus* and *Penicillium*). We showed not only the passive transmission of allergy by fungi, but also, for the first time, provocation with a pure penicillium culture in one of these cases.

If these imperfect fungi, whose spores can easily be cultured, have in certain types of asthma a significant importance which is continually being confirmed, they have a much smaller value in the type of asthma with which we are dealing. Wittich and Stakman<sup>31</sup> proved sensitization to *Ustilago*, and we have shown<sup>14,16</sup> that *Tilletia* is of fundamental importance in the production of this type of asthma. A systematic study, with extract of rusts and smuts of cereals, has abundantly shown us that *Tilletia* is of greater interest, at least in our country, where this fungus is the most frequently encountered grain parasite. Next in importance comes *Ustilago*, and far behind, *Puccinia*; the three cases, in which we have seen clear sensitization, were farmers and not millworkers, a fact which was not surprising when taking into account the conditions of this infection in the ear of corn. In agreement, however, with the results of observations by Waldbott and Ascher,<sup>29</sup> we have found cases of sensitization to *Tilletia*, *Ustilago*, and *Puccinia* in individuals who lived in the country but did not have these occupations. This result may be explained if it can be demonstrated that these spores are in the air. We noted in a paper published some years ago,<sup>18</sup> the existence in the air of *chlamydospores*, the nature of which we were not able to establish.

Today we believe that asthma in millworkers and villagers, and generally in those who live in parts where grains are to be found, is almost always due to sensitization by *Tilletia*,<sup>14,15,16,17</sup> the correctness of which

we have proved not only by means of cutaneous reactions but also by passive transfer and with the provocation tests by nasal contact. Never-

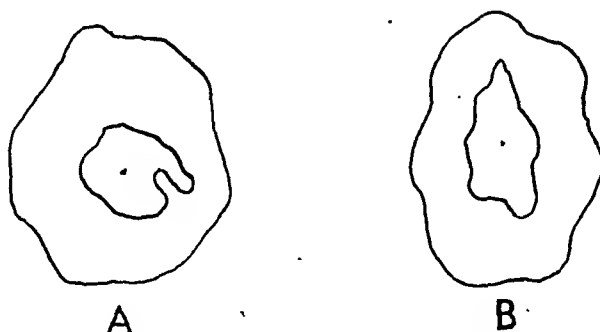


Fig. 1. A and B. Cutaneous reactions.

theless, not all of the cases find a true explanation in the real but infrequent sensitization by flour, in the doubtful sensitization by mites or in the more frequent and proved sensitization by rust and smut. In some cases in which we obtained a positive intradermal reaction and passive transfer to cereal dust, none of these factors gave rise to reaction. Table I, dealing with twenty-four cases of asthma sensitive to cereal dust with positive intradermal reaction (two of them weak), has been reproduced from one of our earlier papers.<sup>12</sup>

Out of this group of twenty-four cases sensitive to cereal dust, proved in many of them by passive transfer, only two were sensitive to flour and of the remaining twenty-two, fourteen were sensitive to *Tilletia*, leaving eight cases which cannot be explained. The possibility remains that we are dealing with independent sensitization that eventually develops owing to variable elements, different in each case, existing in the dust at home. But we made an experiment with the patients, whose result seemed to us very interesting. The first was a man living in the province of Avila and the second a woman living at Ciudad Real, over 200 kilometers away, without any relationship or acquaintance. Both patients had positive passive transfer and reactions to cereal dust but not to clean flour, mites, smuts, and rusts. Notwithstanding, an extract of dust from the granary of one of them (T. Ben.) gave rise to a nasal reaction outbreak in the other (A. Font.). Also, there was a positive reaction in the healthy individual's skin when treated with an injection of serum from the latter patient; the reverse was also positive. We cannot but conclude that the dust taken from these granaries, so far apart from each other, contained an unknown allergen common to both dusts. We had two cases afterwards in which we were able to prove the existence of another source of sensitization: a beetle which frequently parasitizes granaries and corn warehouses.

4. *Calandra granaria*.—A report on the first patient whose case history has allowed us to discuss the possibility, is of interest.

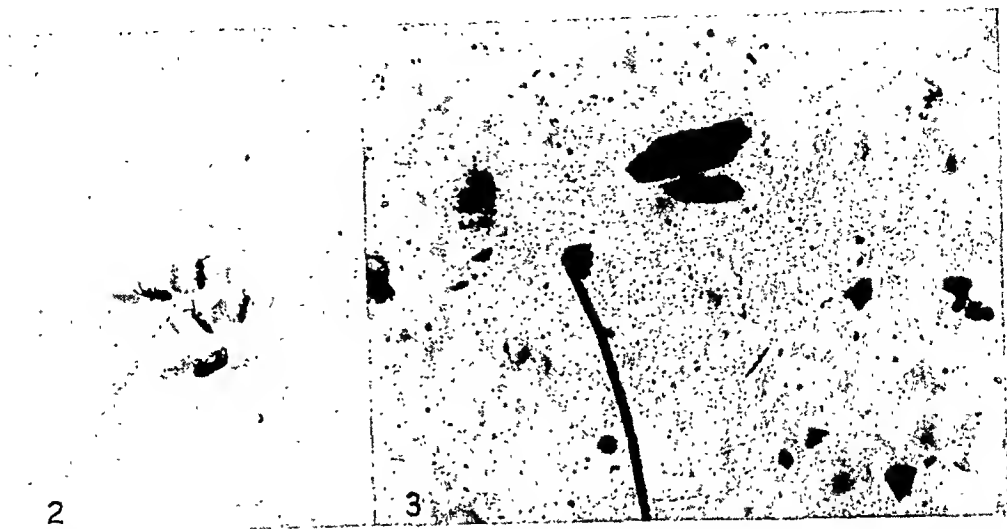


Fig. 2. *Calandra granaria* found in granary dust.

Fig. 3. Granary dust infested with *Calandra granaria*.

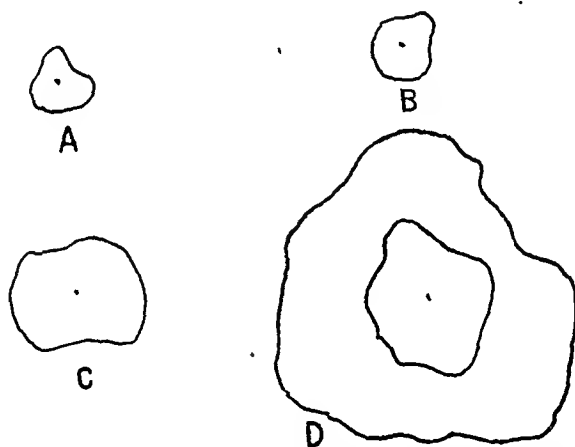


Fig. 4. Passive transfer by Prausnitz-Kustner method. A. Normal serum with control. B. Patient's serum with control. C. Normal serum with extract of *Calandra granaria*. D. Patient's serum with extract of *Calandra granaria*.

P. S. Poz., laborer, forty-six years of age, from the province of Jaen, without having had any previous symptoms, noticed, while packing grain for sowing, itching of the nose and sneezing, a dry cough and acute dyspnea crises that forced him to go out into the open air, where all returned to normal in a quarter of an hour. After some time there also appeared some papular and prurigenous spots (urticaria) on the face, neck, and hands. From this time he began to show similar manifestations whenever he was close to the stored grain. On the other hand, he noticed no reaction with clean grain on the threshing floor. His asthma became so bad that he was in bed two months with "status asthmaticus," and finally came to see us. When he left home he got better, and in Madrid all symptoms disappeared. It is



noteworthy that at home he had grain stored, although it was in another room. Physical examination revealed nothing; the white cell count showed marked eosinophilia (6 per cent). The cutaneous and intradermal reactions with all the series of allergens were negative. The reactions obtained with dust from his granary can be seen in Figure 1. As the reactions to flours, fungi, and so forth were negative, we investigated the dust and found that it was strongly infested (Figs. 2 and 3) with a beetle (weevil) which on being studied turned out to be the *Calandra* (*Sitophilus*) *granaria* (order *coleoptera*; suborder *Polyphaga*; section *Rhyncophora*; family *Curculionidae*) (see Claus, Grobhen, and Kuhn<sup>4</sup>). Extracts of this insect were then prepared, and the intradermal reaction was so acute that we feared for the patient's life. In Figure 1(B), the cutaneous reaction can be seen. The same extract gave no reaction whatsoever when cutaneously or intradermally injected in normal individuals. We then tried passive transfer, the result of which can be seen in Figure 4.

In order to make a complete examination, we carried out the precipitin reaction with our technique which has been published elsewhere,<sup>1</sup> and the following results were obtained:

Precipitins for	Results
<i>Calandra granaria</i>	positive up to 1:640 dilution.
wheat	negative
barley	negative
cereal dust	negative
vegetable dust	negative

Afterwards, we had another case in which this sensitization was accidentally discovered as we had included it among the allergens we commonly test on asthma patients who come from the countryside.

The patient, Sr. A. Ariz., had never had any signs of asthma and had lived in different European and American countries. Three years earlier he retired from business and went to live in a village near Madrid. Every year since then, mainly in autumn and winter, he suffered asthma crises which did not appear when he was out of the village. They were very acute and generally came at night, and he had not noticed any specific causative influence. No positive results were obtained with the reactions to different allergens (foodstuffs, bacteria, fungi, dust from the home, and so on), but when the test was made with *Calandra granaria* extract, an acute asthma attack was produced which necessitated repeated epinephrin injections. Passive transfer was positive and strong.

#### DISCUSSION

We have shown that there exist in cereal dust different elements that, acting as causative allergens, can produce sensitization. In order of importance we can mention among them the fungi, insects, acarina, substances in dust, and flour itself.

The fungi of greatest importance are rust, smut and, especially in our own experience, *Tilletia*. They can be found in great quantities in granary dust and in that of milling establishments, owing to their fineness and the ease with which they spread once the covering of the infected grain has broken. The latter, equally with *Ustilago* and *Puccinia*, can spread in the air at the time of seed-falling, thus acting as causative agents in the population at large (Waldbott and Ascher,<sup>29</sup> and Jimenez-Diaz and co-workers<sup>16</sup>). Other fungi, such as *Aspergillus* and *Penicillium*, can have an

influence above all by infecting damp flour, but this is a much rarer occurrence.

Little account has been taken of insects. Besides occupational asthma, with which we are now dealing, in isolated cases this possibility has been revealed, as in sensitization by *trichoptera* (Caddis fly) (Parlato<sup>21</sup>), *ephemerida* (Figley<sup>6</sup>), *Musca domestica* (Jamieson<sup>11</sup>), *Cimex lectularius* (Sternberg,<sup>24</sup> Jimenez-Diaz and S. Cuenca,<sup>10</sup> and Lahoz and Recatero<sup>20</sup>). Wittich<sup>30</sup> has shown sensitization in cases of vegetable asthma by the *Zabrotes* (bean weevil), and Sheldon and Johnston<sup>23</sup> have shown the possibility of sensitization by *coleoptera*. In the case of asthma produced by granary dust, in farmers or people who live in villages where there are near-by granaries, and also in millworkers, our studies show that the sensitizing agent can be a *colcopteron*, the *sitophilus* (*Calandra granaria*). We believe that in the future more importance should be given to this possibility.

Sensitization to flour is a quality proved and confirmed over and over again, but it is of most importance among bakers; lastly, we can admit the existence of other still unknown substances in dust, such as the generic substance X in house dust.

#### SUMMARY

The authors enumerate the factors existing in grain dust which can act as allergens and be the cause of occupational asthma in millworkers, farmers, and so forth. Besides rust and smut, *coleoptera* must be taken into account (*C. granaria*), and less commonly acarina, flour, and unknown substances similar to those which produce the sensitization action of domestic dust.

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(Continued on Page 553)

## ALLERGY IN GLAUCOMA

### Manifestations of Allergy in Three Glaucoma Patients as Determined by the Pulse-Diet Method of Coca

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**D**URING the past six years we have been conducting an investigation concerning the etiology of glaucoma, especially that of chronic simple glaucoma, in which ocular hypertension is not preceded by other demonstrable ocular pathology. The role of allergy as a possible predisposing factor in this disease, although receiving scant mention in the literature, seemed worthy of consideration. Previous reports<sup>1,2</sup> have dealt with the probable role of bacterial allergy, especially of the upper respiratory tract, in the etiology of chronic simple glaucoma. However, the known methods of establishing allergies, particularly the food allergies, appeared too unreliable to warrant the inclusion of such a study. In 1945 our attention was brought to Coca's method<sup>3</sup> of determining allergy by the pulse rate. We also learned that an investigation of the rôle of allergy in the etiology of glaucoma by Coca and the late Mark Schoenberg had been interrupted by the death of the latter. Although the findings were incomplete, the preliminary results were sufficiently suggestive to justify a more extensive study, especially in view of the fact that glaucoma accounts for at least 12 per cent of blindness in the United States of America.

Difficulty was encountered in the selection of suitable cases. Because of the variability of the signs and symptoms of glaucoma, it was desirable that the patient should have been under our observation for a year or more prior to the allergy study and that he had remained so for at least a year after removal of the allergens. In order to evaluate the effect of the removal of any existing allergens from the diet, or the effect of environment upon the ocular condition, it was considered preferable that the affected eye should not have been operated upon prior to the study, or the tension should have been uncontrolled in spite of surgery. However, a progressive loss of visual fields in spite of apparently controlled tension offered a suitable basis for research. Two of the patients had been operated upon and the tension controlled but they continued to show a progressive loss of visual fields. The latter seemed to show improvement after the institution of an allergen-free diet. In the third patient, no operation had been performed and the tension was not controlled until food allergens were eliminated from the diet. It was essential that the patient have no coronary disease which might interfere with the interpretation of the pulse rate, that existing inhalant or contact allergens be suitably controlled, and, above all,

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Read in the Symposium on Allergy of the Academy of Science, April 26, 1947.

that he be intelligent and painstakingly co-operative. Of fifteen patients with glaucoma, all of whom proved to be allergic by preliminary tests, only three met the specified requirements. All three patients discussed in this paper, received autogenous bacterial antigens developed from their own upper respiratory organisms and were treated by a rhinologist, but their glaucoma was seemingly controlled only after their food allergies, as indicated by the pulse-diet method, received attention.

### Case Report

*Case 1.*—Miss J. L. was observed on May 28, 1945, at the age of forty-four. She had had some watering and burning of her eyes six weeks previously and had been to the Brooklyn Eye and Ear Hospital for treatment. It was there she was first told that a condition of "potential glaucoma" was present. She had no other eye symptoms. Her family history was negative, and past medical history uncovered only the presence of a chronic bronchitis (confirmed by roentgenogram) for several years.

Our examination showed: vision, right eye—20/25 correctable to 20/20 with +1.00D sph. + 0.25D cyl. axis 90°; vision, left eye—20/30 correctable to 20/20 with +1.00D sph. + 0.50D cyl. axis 90°. Accommodation was right eye—600 mm. print at 230 mm., and left eye—500 mm. print at 200 mm. The near point could be brought to normal with a +1.00D sph. added to the above correction.

External and slit lamp examinations revealed no pathologic lesions. Tension taken with a Schiötz tonometer was right: 14 mm. Hg., left: 34 mm. Hg. taken with the 5.5 and 7.5 Gm. weights. Similar readings were found one hour later. Her visual field on the stereo-campimeter was normal. Roentgen examination of the patient's sinuses showed thickening of the mucous membranes of the left antrum and clouding of the sphenoids. There was bone absorption about the roots of her left upper central incisor and right upper lateral incisor.

She was seen by a rhinologist who confirmed the findings in the left antrum, ruling out sphenoid disease by irrigation, and in addition diagnosing the presence of a chronic tonsillitis.

Bacteriological studies revealed that toxic *Streptococcus viridans* was present in large amounts in the throat as well as in the feces. Brucellosis intradermal test was negative but the tuberculin patch test was strongly positive. Basal metabolic rate was minus 9. Her blood count was normal except for a hemoglobin of 76 per cent and a Schilling index of 10.5. Blood chemistry: urea, urea nitrogen, nonprotein nitrogen and cholesterol were above normal.

A buffered solution of pilocarpine 0.5 per cent was prescribed t.i.d. for her left eye, and weekly injections of an autogenous streptococcus vaccine. The tension in her left eye remained elevated on succeeding visits until August 6, 1945, when it was 19 mm. Hg. in each eye. During the interim period she had received treatment to her sinuses, including penicillin locally, by the rhinologist. A visual field taken at this time revealed marked temporal constriction of the left field with a 1 mm. test object. The 2 mm. isopter was normal.

Reculture of the nose and throat on August 9, 1945, again showed toxic streptococci and in addition coliform organisms were found. A coliform vaccine was prepared and given in weekly injections. At this time it was reported that her left upper incisor had been removed and that the sinus infection was "under control."

Observation on October 22, 1945, revealed a change in the visual field of the affected eye. Central fields showed a baring of the blind spot with the 1 mm. object (Fig. 1) in spite of the fact that tension had remained within normal limits.

On December 13, 1945, repeat fecal cultures showed almost complete absence of coliform bacteria and 150,000 toxic streptococci per dry gram. Tension was normal. Chest roentgenogram revealed no disease.

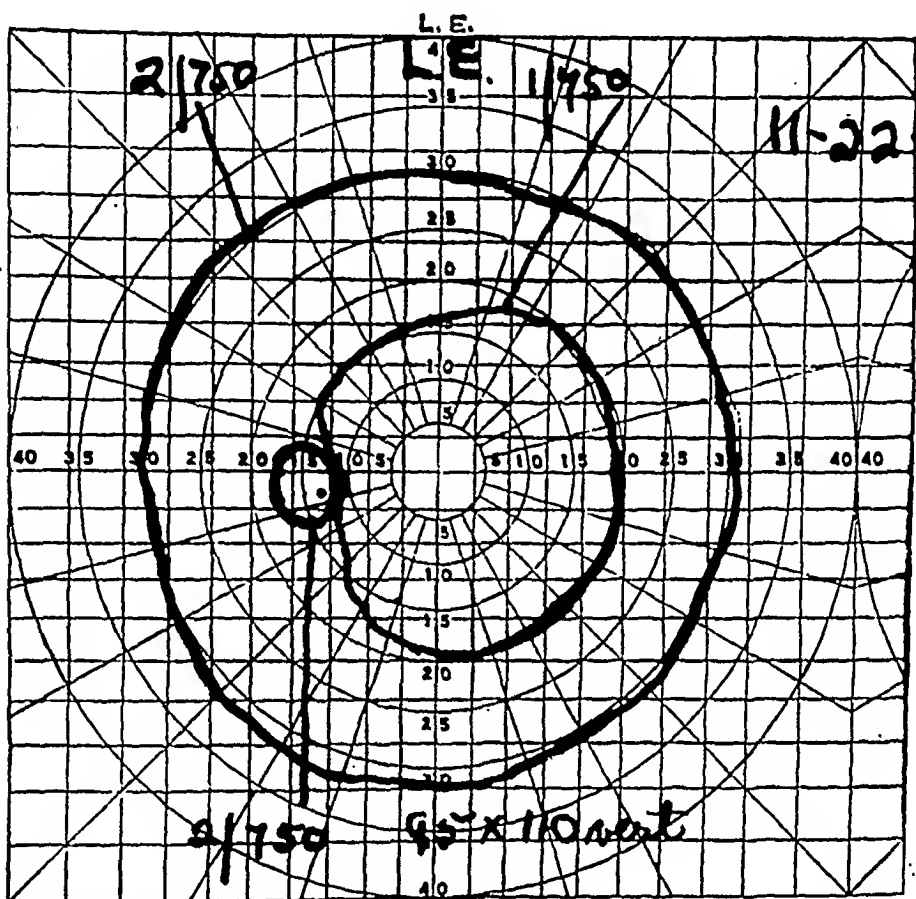


Fig. 1. Left visual field of Mrs. J. L., taken on November 22, 1945, showing temporal contraction of the 1 mm. isopter with baring of the blind spot; 2 mm. isopter is normal.

On January 13, 1946, the patient was started on an allergy study using the pulse-diet method for determining food allergies.

A few days later the patient developed an acute upper respiratory infection which was followed by empyema of the left antrum. This was treated by the rhinologist and on January 25, 1946, he performed an antrotomy. He found a great amount of pus and thickened membranes.

On February 19, 1946, she was placed on a non-allergic diet. The pulse-diet method had shown allergies to potato, cereals, sugar, milk, tomatoes and peanuts.

On March 25, 1946, her visual field again showed baring of the blind spot with the 1 mm. object but a definite improvement over that field taken in October.

She was observed at monthly intervals from March to December with no particular change in the tension. Repeated visual fields remained the same.

On April 15, 1947, after an absence of four months during which time she remained on her allergen-free diet and received her autogenous streptococcus and coliform vaccines, her visual field showed improvement over previous fields. There was no baring of the blind spot in the left eye and the 2 mm. isopter was normal (Fig. 2).

*Follow-up and Highlights.*—This case is not so dramatic as the other

two cases we shall report because the ocular condition before starting the allergy study was not so serious. Her tension was brought under control by pilocarpine before the allergen-free diet was instituted. Her vision

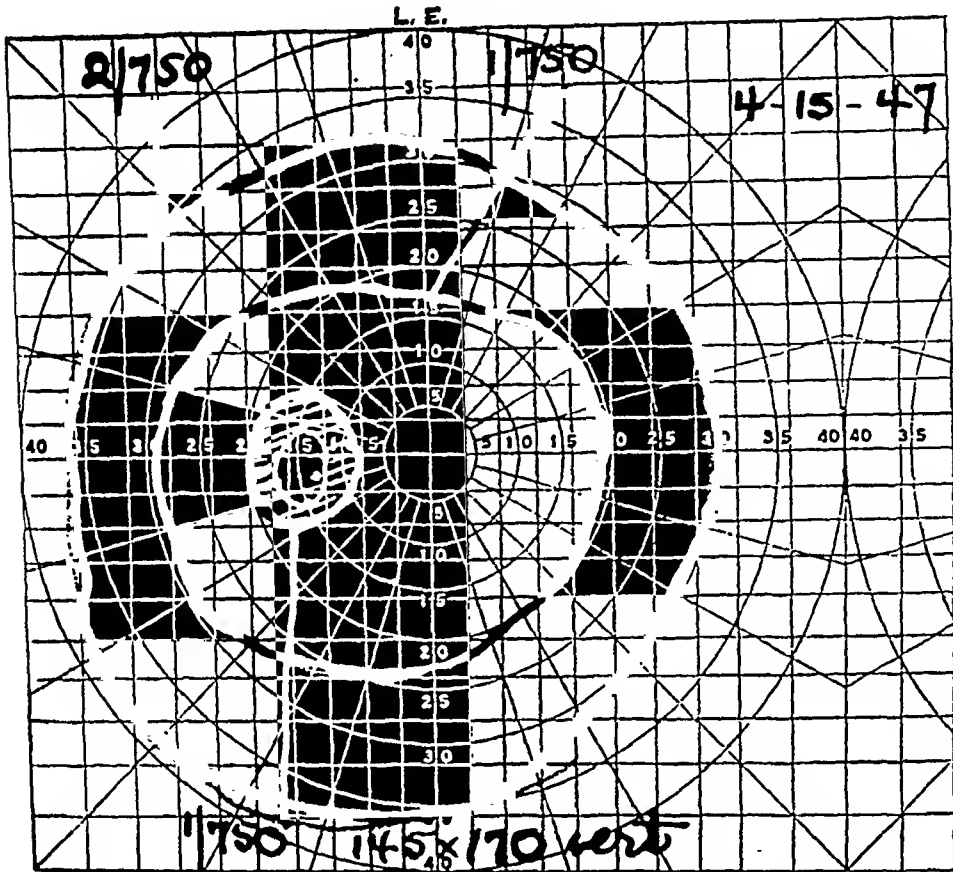


Fig. 2. Left visual field of Mrs. J. L., taken on April 15, 1947, showing improvement of 1 mm. isopter and no barring of the blind spot.

is and was approximately normal with slight fluctuations. Visual acuity is usually the last ocular function to be affected in glaucoma.

Two visual fields taken after going on the non-allergic diet were normal, whereas before the institution of the diet there was progressive constriction of the smaller isopters with barring of the blind spot. This was the most marked ocular improvement.

Associated symptoms of chronic constipation completely disappeared after the institution of the diet.

*Case 2.*—Mrs. I. E., aged forty-six, was first observed on December 12, 1943. She had been treated four years previously for glaucoma of her right eye. She was complaining of sharp pain over her right eye.

Examination: Vision corrected, right eye—HM at 1 foot; left eye—20/15. The right eyelids were edematous and red, the bulbar conjunctiva was deeply congested.

The anterior chamber was shallow, the pupil was dilated and fixed. There was typical glaucomatous cupping of the optic disc (8 diopters) and pallor of the nerve. Tension with Schiötz tonometer right eye 30 mm. Hg., left eye 12 mm. Hg.

Her visual field was reported as: right eye, light field at 2 inches, only small temporal field of perception nasally, above and below. Left eye, slight contraction above and below nasally with 1 mm. object. Absolute scotoma above the blind spot with 1 mm. object. Blind spot enlarged.

Roentgen examination of her sinuses revealed slight clouding of the ethmoids, and marked clouding of the left antrum with thickening of the mucosa. There seemed to be fluid in the right antrum. The sphenoids were cloudy, the right more than the left.

The rhinologist verified the fact that there was infection in the sinuses and advised sulfadiazine treatments by the Proetz method.

Hematology studies were reported as normal except for a high Schilling Index (38).

Cultures taken from the nose, throat and feces showed *B. coli* and *Strep. viridans* in the throat, and highly toxic (to *in vitro* tests) *Streptococcus viridans* in the feces.

A 2 per cent solution of pilocarpine was prescribed for the right eye q.i.d. and weekly injections of an autogenous coliform vaccine advised. She was treated simultaneously for her sinus infection.

In spite of this treatment, she returned two weeks later in acute distress with her right eye. Examination showed her tension had risen to 56 mm. Hg. in that eye. She was treated in the office with pilocarpine 2 per cent and eserine packs. This failed to lower the tension perceptibly and she was given a retrobulbar injection of 1.5 c.c. of 2 per cent novocaine. Her tension dropped to 40 mm. Hg.

Within another two weeks her tension had again risen to 60 mm. Hg. in her right eye and she was admitted to the hospital.

On January 21, 1944, under local anesthesia, an iridocorneosclerectomy was performed on the right eye. Postoperative recovery was uneventful. Her tension remained subnormal for one month and then began to gradually rise. Her visual field in the right eye taken on March 24, 1944, showed a small area of vision in the lower temporal field taken with the 20 mm. object. Her light field was slightly larger. The left visual field was unchanged.

During the next week her tension gradually rose in spite of increasing strengths of pilocarpine and eserine. On April 3, 1944, it was recorded as right eye—56 mm. Hg., left eye—19 mm. Hg. On April 4, 1944, iridocorneosclerectomy and iridencleisis were performed. Following this procedure the tension in her right eye stayed down only two weeks and again rose to 47 mm. Hg., necessitating a retrobulbar injection of alcohol. Her tension fell to normal (23.5 mm. Hg.) but during the next month demonstrated a progressive rise and remained high but the eye was not painful. The tension remained high for several months and then fell to normal.

In October, 1945, her tension again began to rise, this time not only in the almost-blind eye, but in the good left eye as well. (Right eye—34 mm. Hg, left eye—32 mm. Hg.). Her visual field at this point was reported as: right eye—small seeing area with 20 mm. object and light temporally; left eye—temporal contraction of the 1 mm. isopter with baring of the blind spot.

In an effort to determine the cause of the continuing hypertension and contraction of the visual fields and thereby retain the vision in the left eye, allergy studies were made by the pulse-diet method of Coca. Major food allergies were found to be: chicken, peas, beans, peanuts, lettuce, wine, eggs, cauliflower, cabbage, brussel sprouts and broccoli.

Two weeks after being placed on an allergen-free diet, this patient's tension, using the same strength of pilocarpine, taking the tension at the same time of day and

# GLAUCOMA—BERENS, GIRARD AND CUMMINGS

after the same post-miotic interval, was recorded as within normal limits (right eye—25 mm. Hg., left eye—25 mm. of Hg.). Five weeks later the tension was right eye—17 mm. Hg., left eye—20 mm. Hg.

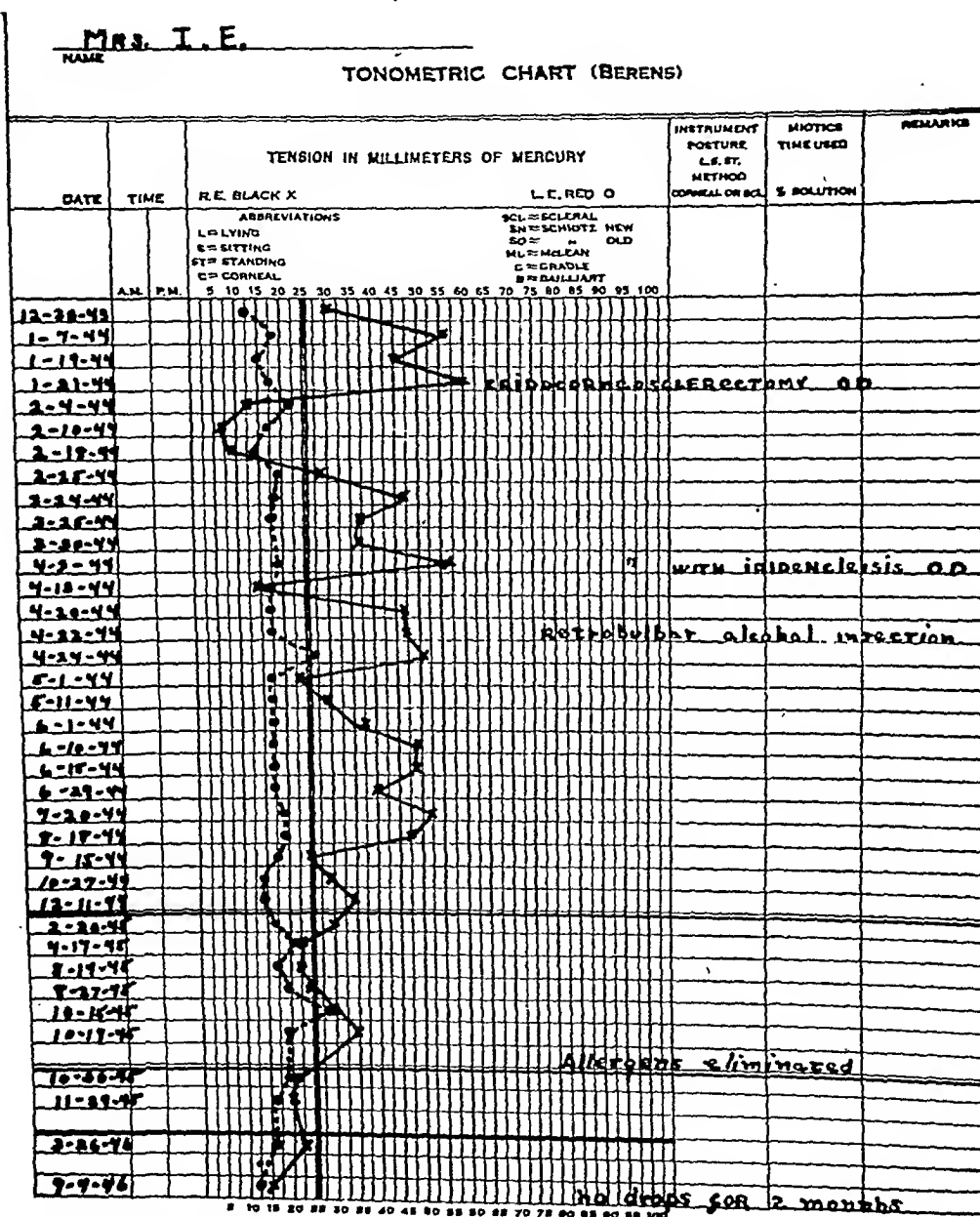


Fig. 3. Tonometric chart of Mrs. I. E. Note that tension remained normal for one year after the elimination of allergens.

She was not observed again until September 4, 1946, when after using no pilocarpine for two months previously, her tension was right eye—16 mm. Hg.; left eye—13 mm. Hg. Vision was right eye—HM; left eye—20/15 with correction.

*Follow-up and Highlights.*—This patient had glaucoma of both eyes with uncontrolled tension in her right eye in spite of repeated operative



intervention and intensive medical therapy. There was beginning hypertension in the left eye. Following the institution of an allergen-free diet, the tension became normal in both eyes even after cessation of all medication (Fig. 3).

Associated allergic symptoms were severe gastrointestinal distress and chronic constipation. Within two weeks after adhering to the allergen-free diet and without the customary cathartics, the patient's elimination was normal for the first time in the patient's memory.

It is a recognized fact among most ophthalmologists that emotional stress or worry has a direct effect on the ocular tension of the glaucomatous patient. In this particular case, at least some of the tension rise during the stormiest period could be attributed to the patient's worry over, and subsequent loss of her brother (about the time of the retrobulbar injection). Another similar experience would be expected to have a similar result, yet, during 1946, while on her allergen-free diet, the patient went through a severe emotional and physical experience involving the near fatal illness of her only son. With special permission from the Navy Department she nursed him eight to ten hours a day for three months. At no time did her eyes bother her, nor was there any rise in tension in spite of not using miotics. Since glaucomatous patients usually are as dependent on miotics as diabetics are on insulin, it was a good test of the possible benefit resulting from the allergen-free diet.

*Case 3.*—Miss E. H., aged sixty-seven, a retired school teacher, was examined on March 3, 1941. On her first visit her vision was right eye—20/100 correctable to 20/20 with + 2.25D cyl. axis 100°; left eye—20/100 correctable to 20/20 with a + 2.25D cyl. axis 85°. With a + 2.50D added to the above correction, she could read 400 mm. print at 290 mm. with each eye. Her tension was recorded as right eye—40 mm. Hg.; left eye—26 mm. Hg. with the Schiötz tonometer and a 7.5 gm. weight. The anterior chamber of each eye was shallow, otherwise the external examination was normal. Both lenses showed finely granular cortical opacities.

Her visual field was recorded as right eye—slight enlargement of the blind spot, slight concentric contraction with 1 mm. test object, and slight contraction for all colors; left eye—enlarged blind spot and temporal and inferior contraction with 1 mm. test object.

Her general physician reported a right radiculitis and a hypertrophic cervical arthritis.

Laboratory studies revealed a moderate secondary anemia with a sedimentation rate of 18 mm. per hour and a Schilling Index of 62. Cultures from her nasopharynx demonstrated numerous toxic hemolytic streptococci and *Streptococcus viridans*.

The patient was placed on pilocarpine 2 per cent b.i.d. for her right eye and hot compresses and massage for both eyes. Under this regime her tension came down and remained within normal limits for seven months. During this time she had no pain but complained of attacks of blurring of vision in her right eye. Her visual field remained approximately the same and she was placed on an autogenous streptococcus vaccine.

On November 10, 1941, she complained of acute pain in her right eye following a severe cold. Her vision in the right eye was 3/200; her tension was right eye—44 mm. Hg.; left eye—14 mm. Hg. with the 7.5 gm. weight. Her last pilocarpine

drops had been taken only two hours previous to the examination. Under the slit lamp the cornea showed clouding and the iris was congested.

She was placed in the hospital and an iridocornesoclerectomy performed that same day. Her postoperative recovery was good but her corrected vision in her right

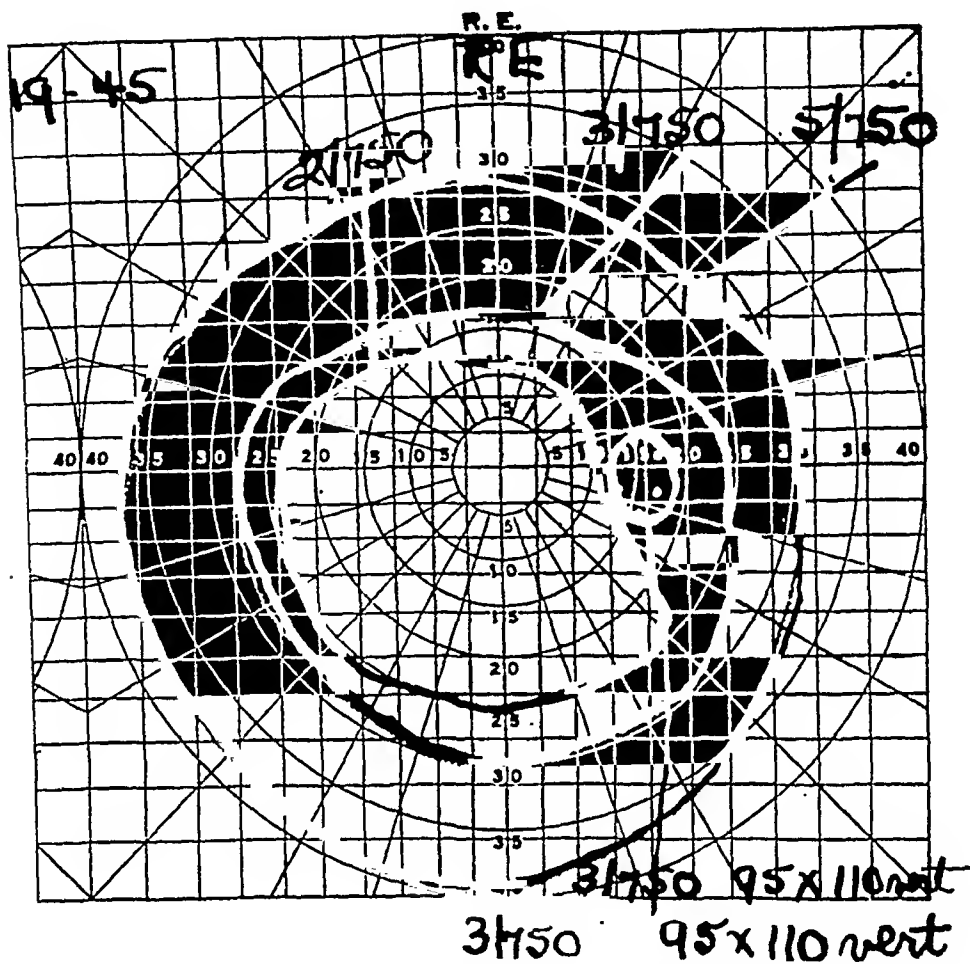


Fig. 4. Right visual field of Miss E. H., taken on October 19, 1945, showing marked temporal contraction of all isopters and baring of the blind spot.

eye was reduced to 20/100. She was observed periodically during the next two years. Her tension remained normal but her vision continued to be poor in the right eye. Repeated visual fields continued to show contraction of her right field. Toward the end of this period her vision began to fail (going down to 20/200 in her right eye) and there was progressive contraction of her visual fields.

At this point (September, 1945), the patient was investigated for possible food allergies. These studies covered a period of approximately two months. The pulse-diet method revealed the following major allergens: wheat, all cheese, oatmeal, coconut, pork (including jello with a pork base), vinegar and citrus fruits and Lavo's. Questionable allergens included beans, milk, lettuce, V-8 vegetable juice, the apric family and coffee.

The patient claimed subjective general and visual improvement soon after she was placed on the allergen-free diet.

Her last field before starting the allergen-free diet was taken on October 19, 1945. It was similar to those taken previously showing upper temporal loss in all isopters and baring of the blind spot (Fig. 4).

In November, 1945, there was definite improvement in the visual field of the right eye for the 3 mm. isopter and slight improvement in the 2 mm. isopter.

Six months later, June, 1946, the improvement was even more marked, 2 and 3 mm. isopters had filled out and there was no longer a barring of the blind spot.

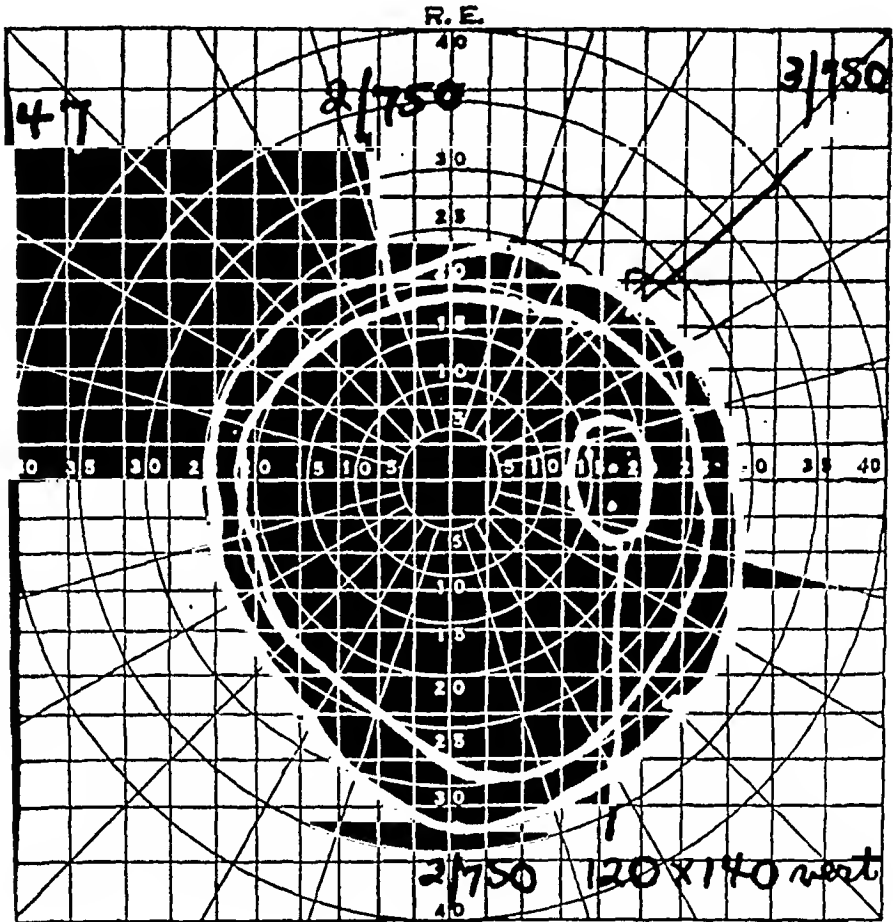


Fig. 5. Right visual field of Miss E. H., taken on February 14, 1947, showing normal 2 mm. and 3 mm. isopters and no barring of the blind spot.

The last field taken on this patient was on February 14, 1947, (Fig. 5) and was the most normal field taken since the onset of the patient's glaucoma.

*Follow-up and Highlights.*—The patient was placed on her non-allergic diet on December 20, 1945. On January 4, 1946, her vision in the right eye was 20/200, but on January 31, 1947, it had risen to 20/100 and it has remained at this point up to the present in spite of an increase in density of the cataract in that eye.

The field taken on June 6, 1946, six months after initiating the allergen-free diet showed a definite improvement over the previous fields. This was an unusual finding since loss of visual fields associated with optic

nerve damage is usually irreversible. The most that can be hoped for usually is the maintenance of the field without further loss.

Fields were taken on February 14, 1947, and further improvement over June was noted.

It is important to state that the technician who took these fields was the same one who had previously taken them during the two-year period when a progressive loss was observed. Also, the tests were standardized as to lighting (7.5 foot-candles), the size of the test objects, and other factors.

It was also interesting to note that other allergic symptoms, i.e. chronic rhinitis, coughing attacks after meals, eczema, chronic constipation with flatulence and gastrointestinal distress, and neuralgic pains in the neck and face were no longer complained of after the institution of the allergen-free diet.

It may be mentioned that in July, 1945, this patient made application for assistance in learning Braille and for entering a home for the blind. Her psychologic reactions have so improved that she has now abandoned these ideas.

### Summary

Three cases of chronic simple glaucoma have been presented in which the usual treatment with miotics and attempted desensitization with autogenous bacterial antigens had been supplemented by the removal from their diets of food allergens, as determined by the pulse-diet method. In one case, the hitherto uncontrolled tension was brought under control apparently only after the institution of an allergen-free diet. In the other two cases, surgery and medical treatment controlled the glaucomatous hypertension but failed to check progressive loss of visual fields. The latter showed marked improvement after the institution of an allergen-free diet.

In view of the many uncontrollable factors involved in the treatment of glaucoma from the psychological, medical and ocular viewpoints it is inadvisable to draw definite conclusions. However, because of the suggestive findings in these cases, it was thought warranted to report them with the hope that the possible role of allergic factors in glaucoma will be investigated by others and the effect of anti-allergic treatment of this most serious disease will receive final evaluation.

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## ANTI-ASTHMATIC EFFECTS OF A NEW SYNTHETIC ANTISPASMODIC

### Beta-Diethylaminoethyl 9, 10-Dihydroanthracene-9-Carboxylate Hydrochloride

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SINCE bronchospasm is part of the disordered physiology of asthma, clinicians are interested in new antispasmodics. If the spasmolytic agent is one which counteracts many of the pharmacologic effects of histamine, indicted as the intermediary between antigen-antibody reactions and clinical manifestations, that interest is doubly keen. Such a compound is Beta-Diethylaminoethyl 9,10-Dihydroanthracene-9-Carboxylate Hydrochloride, hereafter more simply referred to as Compound No. 887.

Antispasmodics are of two general types<sup>6</sup>: Those which are musculotropic, such as the nitrites and papaverine, are tested pharmacologically against histamine phosphate ( $2 \times 10^{-6}$  gm./c.c.) and barium chloride ( $10^{-4}$  gm./c.c.). Those which are neurotropic, such as atropine and scopolamine, are tested against acetylcholine bromide ( $10^{-6}$  gm./c.c.). The more peripherally acting musculotropic group would be of most interest to the allergist even without the concept of histamine antagonism. Marked bronchospasm can also contribute to mucosal edema by impairment of lymphatic drainage.<sup>2</sup>

Combinations of various amino-alcohols and chemical modifications of diphenyl-acetic acid have been known to be antispasmodic. The amino-alcohol determines the nature of the action, while its intensity is modified by the acid group employed. Many of these compounds have local anesthetic action, which appears to correlate more closely with musculotropic action than with other properties.<sup>4</sup>

Compound No. 887 is a pure white crystalline substance with a melting point of  $170^{\circ}$  C. Its basic alcohol, beta-diethylaminoethanol, is a well known compound. The acid, 9,10-dihydroanthracene-9-carboxylic acid, is prepared as follows<sup>1</sup>: A solution of n-butyllithium, prepared in the usual manner from 127.4 gm. (0.93 mole) of n-butyl bromide and 10 gm. (1.44 atoms) of lithium in 1,000 c.c. of absolute ether, is siphoned under a stream of nitrogen into a stirred suspension of 82 gm. (0.45 mole) of 9,10-dihydroanthracene in 400 c.c. of ether. The rate of addition of the butyllithium solution is regulated to produce moderate refluxing. The mixture is then stirred for one hour at laboratory temperature and finally refluxed for three hours. Carbonation with crushed dry-ice, followed by extraction with water and acidification, yields 77 grams of the desired acid, melting at  $203^{\circ}$  to  $204^{\circ}$  C. Combination of the acid with the chloride of the amino-alcohol to form the desired ester is carried out in isopropanol solution (Fig. 1).

The resulting ester No. 887 is, in general, twenty times more potent than papaverine and one-fifth as effective as epinephrine in relaxing

The product used in these investigations was supplied through the courtesy of G. D. Searle & Co.

# NEW SYNTHETIC ANTISPASMODIC—HARTMAN

spasm of the bronchioles induced in experimental animals by histamine.<sup>1</sup> Guinea pigs are protected against death from intravenously administered histamine, and spasm of the guinea pig ileum is relaxed.<sup>5</sup> Perfusion of the guinea pig lung produces bronchodilation. Bronchoconstriction in bar-

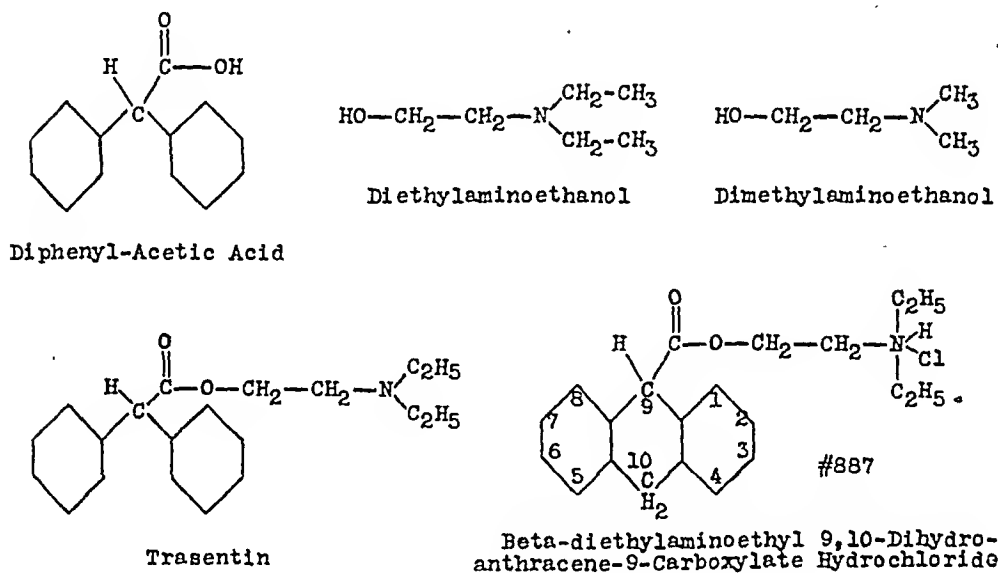


Fig. 1. Structural relationships of Compound No. 887.

bitalized dogs from both acetylcholine and histamine is antagonized. The vasodepressor effect of intravenous histamine is reduced at least 50 per cent by pretreatment with Compound No. 887. The vasopressor effect of epinephrine in cats is reduced and may be reversed. Local anesthetic action is well demonstrated on the rabbit's cornea. A central hypnotic action, minor in animals, is significantly present in humans.

The following data on toxicity were derived from animal experimentation.<sup>3</sup> The LD<sub>50</sub> dose, (fatal to one-half of the animals used) was determined by various methods, listed below:

Rats—Intraperitoneal Injection	LD <sub>50</sub> 0.18 gm./kg.
Rats—Stomach tube	LD <sub>50</sub> 1.10 gm./kg.
Mice—Subcutaneously	LD <sub>50</sub> 0.60 gm./kg.
Mice—Intraperitoneal injection	LD <sub>50</sub> 0.17 gm./kg. (0.16)*
Mice—Stomach tube	LD <sub>50</sub> 0.45 gm./kg. (0.425)*
Mice—Intravenously	LD <sub>50</sub> 0.027 gm./kg. (0.017)*

Using the lowest LD<sub>50</sub> dose found in animals by the stomach tube method (0.45 gm./kg.) as a basis for calculation of the human LD<sub>50</sub> dose, one would arrive at a figure of 31.5 gm. for a 70 kg. adult. Inasmuch as the dosage used clinically should rarely exceed 0.2 gm. orally, there is a very evident large margin of safety.

\*Figures in parentheses are from an earlier and smaller series.

## CRITERIA EMPLOYED IN CLINICAL TRIALS

The following objective criteria for the relief of asthma were employed: disappearance or marked diminution of rhonchi; relief of dyspnea with shortening of the phase of expiration; increase in vital capacity.

The subjective criteria used were: diminution or disappearance of wheezing, shortness of breath and coughing; ability to sleep horizontally after previous orthopnea; enjoyment of nights of rest after previously consistently disturbed nights.

During these investigations a definite effort was made to exclude that 25 per cent of asthmatic patients who admit or claim temporary benefit of some degree from any medication, however inert.

## OBJECTIVE DETERMINATION OF MINIMUM AND OPTIMUM EFFECTIVE DOSAGE

In the first group of thirty adult ambulatory asthmatic patients an effort was made to determine the minimum and optimum effective dosage. The types of asthma represented were the extrinsic, the intrinsic, and the combined; the sexes were equally represented.

A dosage of 0.1 gm. every four hours was prescribed, with the following results:

Complete relief .....	8 (Group 1)
Partial relief .....	4 (Group 2)
No relief .....	18 (Group 3)
Total .....	30 Cases

In the completely relieved group of eight, seven had some sedative effect, variously described as calmness or "dopiness." Three of the non-relieved were similarly affected. No vertigo or nausea was reported.

The dosage was then raised to 0.2 gm. every four hours in each of the above subgroups. The first group continued to manifest complete relief, but the sedative effect was heightened in every case, so that only five of the eight were able to perform their usual tasks without falling asleep. The other three fell asleep during the day. One instance of vertigo was encountered.

The four patients in Group 2, partially relieved before, were now completely relieved, but experienced varying degrees of sedation or hypnosis. One instance of nausea occurred.

An additional thirteen of the previously unrelieved eighteen in Group 3 now experienced more or less relief of asthma, but the number noting hypnotic effects increased from three to seven. One instance each of nausea and dizziness was encountered.

The five persons who received no relief from the 0.2 gm. dose were given 0.3 gm. and then 0.4 gm. doses without relief but with marked vertigo or sleepiness.

It was evident that the administration of more than 0.2 gm. every four hours was not necessary. At this dosage level, twenty-five of these thirty

## NEW SYNTHETIC ANTISPASMODIC—HARTMAN

patients were relieved of their coughing and wheezing, but sixteen of the twenty-five relieved, experienced various degrees of sedation or hypnosis. At the 0.1 gm. dosage level twelve of these same thirty patients were relieved, seven of the twelve noting some sedative effect. It also became evident that the hypnotic effect, desirable as it might be during hours of sleep, limited the usefulness of the drug during the day.

### SUBJECTIVE DETERMINATION OF OPTIMUM DOSAGE

The next group of thirty asthmatic patients, consistent with the first, were told about the dual nature of the drug and were asked to determine their individual optimum dosages, with consideration both to relief of asthma and sedation. These are the assembled reports:

0.2 gm. every four hours .....	6
0.2 gm. on retiring but only 0.1 gm. every four hours during the day .....	5
0.1 gm. every four hours .....	7
0.2 gm. at bedtime only .....	4
0.05 gm. every four hours .....	2
No relief at any dosage up to 0.3 gm. every four hours .....	6
Total .....	30 cases

The approximate 80 per cent more or less relieved paralleled the first series. The patients when left to their own discretion had a tendency to use the 0.2 gm. doses on retiring and the 0.1 gm. doses during the day.

The conclusions to be reached from the study of the sixty moderately severe but ambulatory cases of asthma in these two groups were: (1) that approximately 80 per cent received appreciable to complete symptomatic relief from Compound No. 887 taken orally, (2) that the effective dosage varied from 0.1 gm. to 0.2 gm. every four hours, and (3) that the hypnotic effect limited the use of the larger doses in the individual case.

### EFFECT IN STATUS ASTHMATICUS

The drug was employed as the sole medication in six cases of status asthmaticus, with complete relief in two cases and partial relief in two others. Since these patients were bedridden and under close observation, a dosage of 0.2 gm. every two hours was used initially in every case. In the two cases completely relieved, this dosage had to be reduced after a day to 0.2 gm. every four hours. The two patients partially relieved had their dosage similarly reduced after thirty-six hours because other remedies were added, and after the third day the administration of Compound No. 887 was discontinued. The two patients unrelieved after one day were changed to other medication.

### EFFECT ON ASTHMATIC CHILDREN

Nine children between the ages of five and nine were treated with doses proportionate to their body weight based on 0.2 gm. for a 70 kg. adult. The percentage of symptomatic relief paralleled the adult series, seven



of the nine being benefited. The hypnotic effect seemed more marked, and two instances of nausea and four of "dizziness" occurred. Two of these "dizzy" children presented muscular in-coördination and slurred, incoherent speech.

#### COMPARISON WITH A STANDARD SEDATIVE-ANTISPASMODIC COMBINATION

A group of fifteen adults having regular nocturnal attacks only were subjected to the following experiment. Every night of the first and third weeks they took 0.1 gm. sodium pentobarbital and 0.2 gm. aminophylline at bedtime. Every night of the second and fourth weeks they took 0.2 gm. of Compound No. 887 at bedtime. The object was to ascertain how effective Compound No. 887 was as a combined antispasmodic and sedative compared to a standard combination of known efficacy.

Compound No. 887 preferred .....	7
Sodium pentobarbital-aminophylline preferred .....	4
No preference .....	4
	<hr/>
Total .....	15 cases

#### EFFECTS OF PROLONGED ADMINISTRATION

Five patients who used the drug constantly and four patients who used it intermittently in doses of 0.1 or 0.2 gm. four times daily were followed for three months with fortnightly urinalyses, complete blood counts, and fasting blood nonprotein nitrogen determinations. Nothing other than the slight normal variations usually found was noted. Of interest to allergists was that no change in the total number or percentage of eosinophiles occurred in any case.

Six patients taking 0.2 gm. each night were followed for five weeks with the same check-up at weekly intervals, and no significant variations were encountered. In none of these eleven cases was there an instance of either habituation or loss of tolerance to the drug.

#### SUMMARY AND CONCLUSIONS

The author's conclusions, based on ninety cases treated orally with Beta-Diethylaminoethyl 9,10-Dihydroanthracene-9-Carboxylate Hydrochloride (Compound No. 887) is that it is a safe and useful anti-asthmatic remedy, combining antispasmodic and sedative action. The latter effect somewhat limits its usefulness for daytime use, but it is a valuable feature at night because of the tendency of asthma attacks to occur more frequently or only at night. A dose of 0.2 gm. every four hours rarely need be exceeded, and half that may suffice. A bedtime dose of 0.2 gm. furnishes acceptable symptomatic relief to the majority of people suffering from nocturnal attacks only. The only important side-effect is

*(Continued on Page 593)*

## METHODS FOR THE OBJECTIVE DEMONSTRATION OF SUSPECTED DRUG SENSITIVITY

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IN medical practice there often arises the problem of deciding whether a patient's fever, skin eruption, or leukopenia represents an allergic reaction to a certain medication or is an integral part of the disease from which he is suffering. The treatment, diagnosis and ultimate prognosis may rest upon the answer.

This question has faced us repeatedly. All too often we have not been able to answer it satisfactorily. For this reason, we believe that a review of the fundamental nature of the problem is in order, and also an analysis of the techniques which may lead to its solution.

It is essential to limit this discussion to the true manifestations of hypersensitivity. We are not concerned with those reactions which are due to an exaggerated pharmacologic action of a drug. These are toxic reactions and do not represent true allergic states. We are concerned only with those responses which follow prolonged or repeated administration of a therapeutic agent and result in known allergic symptoms, i.e., urticaria, atopic eczema, asthma, et cetera. Bronfenbrenner<sup>3</sup> in 1943 summarized the reasons why such drug reactions should be classified as true allergies.

The only real reason for separating this group of reactions from the other forms of hypersensitivity is *the nature of the antigen*. The antigen is usually not a protein. The antigenicity of these compounds was proven by the fundamental work of Landsteiner on haptenes.<sup>9</sup> Countless simple chemical substances have been shown to be capable of forming antigenic combinations with proteins. It is highly probable that the sensitizing antigen in drug allergy is a drug-protein combination which results from a conjugation with one of the plasma protein fractions.

*Allergic disorders* produced by the oral administration of drugs are very similar to those produced by sensitivity to foods. Like foods, the oral drug is subject to alteration by the acidity of the stomach, the digestive enzymes, the bacterial flora of the intestinal tract, and the processes of absorption. The simpler drugs are absorbed unchanged. The more complex drugs undergo extensive changes, and the substance finally absorbed may bear little or no resemblance to the original compound. The antigenic properties of this product may vary in antigenic specificity from that of the original drug.

Once absorbed, the compound may be split into simpler units or may be conjugated with other substances. The sulfonamides are acetylated, sodium benzoate is detoxified by glycine. The absorbed drug compound

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Read before the Southeastern Allergy Association, January 18, 1947.

can combine with the plasma proteins. Iodine fractions, for instance, may be free or protein-bound. Lastly, there is always the possibility that the drug itself may not actually be a part of the final antigen; this antigen may be some other constituent of the organism which has been specifically altered by the action of the drug. For example, acetanilid may change hemoglobin to methemoglobin or sulfhemoglobin.

There are many reasons, then, why an individual may fail to provide a positive skin test when phenolphthalein is injected into the skin even though the oral administration of this substance produces a violent, bulbous erythema multiforme.

To demonstrate drug allergy, the individual problem must be carefully analyzed. The proper method of study can only be determined after the probable pathogenesis of the allergic syndrome is clearly understood. Each drug-sensitive patient must be approached as a new problem, a problem which only in its broadest outlines resembles problems which have been encountered before. There can be little hope of developing a blanket routine which will invariably prove a suspected drug hypersensitivity.

*Skin tests.*—A positive skin test is dependent upon the reaction of a specific antigen and antibody in the presence of an indicator tissue. In drug sensitivity it may be anticipated that the true antigen will often be difficult to obtain and utilize. However, in the majority of instances, the identity of the offending agent will be suspected. Wholesale testing will rarely be necessary.

As in other forms of haptene sensitivity, the drug alone may provoke a reaction in a skin sensitive to a drug-protein combination. *In vitro* mixtures of drug and serum or plasma proteins may contain a satisfactory antigen. The serum of individuals receiving the drug in therapeutic or greater quantities may contain the antigenic substance. It may also be possible to synthesize the antigen and then use it for direct skin testing.

The peculiarities of the antigen then make it difficult to develop skin tests for drugs. It may be more profitable to approach the problem by means of the antibody. It is reasonable to expect that at some time the plasma of sensitive individuals will contain the specific antibody. Experiments on sensitivity to simple chemical compounds have shown that these antibodies are present in very low concentration. They are strongest in the plasma a few hours after exposure to small amounts of antigen.

*The passive transfer method* of testing offers several possibilities. The most straightforward method is the injection of the prepared site with the suspected antigen preparations. The technique developed by Walzer for the detection of the absorption of undigested proteins<sup>14</sup> offers interesting possibilities in that it closely approximates the actual conditions encountered in sensitivity following ingestion of drugs. The serum supposed to contain the antibody is injected into the skin and the drug is then

administered by mouth. This drug would then be subject to all of the processes of digestion, absorption and metabolism which might naturally occur. By the time it reached the prepared site it would stand a good chance of closely approaching the true antigen and, perhaps, of producing a positive reaction. The metabolic processes which influence the antigen may take some time (forty-eight to seventy-two hours) and the skin reaction can be expected to be delayed.

What, then, has been the experience with these more or less standard diagnostic approaches to hypersensitivity when applied to drug allergy? Our own studies are still in the preliminary phase. The literature contains many reports of the successful and unsuccessful application of methods of study.

The *patch test* is occasionally successful. It utilizes the pure drug as antigen. The test is likely to be positive in cases with cutaneous manifestations of hypersensitivity and, of course, contact dermatitis. If the skin is highly reactive, the primary irritating properties of the drug may produce a false positive test. A negative test is of no significance except in the contact sensitivities.

The *intradermal test* with the unaltered drug is roughly comparable to the patch test and is one of the least satisfactory methods for the demonstration of drug allergy.

The *tongue test* suggested by Duke<sup>5</sup> for use in cases of aspirin hypersensitivity consists of placing a small quantity of aspirin on the tip of the tongue. When positive, symptoms occur within one minute. Absorption is stopped by rinsing the mouth with vinegar or dilute acetic acid. This test is worth trying with other drugs. It is of no value in such disturbances as erythema multiforme, drug fever, or agranulocytosis where no immediate symptoms can be expected.

Blank<sup>2</sup> succeeded in demonstrating sensitivity to aspirin, sulfadiazine, sulfathiazole, and codeine by holding a tablet of the drug against the *buccal mucous membrane* for ten to twenty minutes.

The immediate reaction is edema and perhaps vesiculation. The twenty-four-hour reaction is vesiculation.

The *conjunctival test* has been used occasionally with success. This method seems to be particularly useful in demonstrating sensitivity to diodrast before it is given intravenously.

The *depression of the blood leukocyte count* following the ingestion of an allergen has been used as a method to test for food hypersensitivity.<sup>7</sup> This procedure may be applicable to drug allergy. So far there are no reports of its use in the literature. In a single instance of lipiodol hyper-

sensitivity, we observed no change in the total or differential leukocyte counts following oral administration of iodine.

The only other test of value utilizing the unaltered drug is the absolute *test of readministration*. If a given syndrome is caused by an allergic reaction to a non-protein medication, it is inconceivable that the identical readministration of the drug should fail to reproduce the syndrome. This method is simple and decisive. When dealing with minor allergic syndromes which do not endanger life or threaten permanent damage to the individual, it is superfluous to waste time and effort with other, more elaborate forms of testing.

Tests utilizing *mixtures of drug and blood serum* have been especially promising. Two types of such preparations have been tried: those obtained *in vitro*, and those provoked *in vivo*. Dameshek and Colmes<sup>4</sup> and Austin<sup>7</sup> prepared an antigen by mixing a solution of aminopyrine with serum, and allowing it to age at 4° C. This antigen gave positive intradermal reactions in patients with agranulocytosis caused by aminopyrine.

Hypersensitivity to the sulfonamide drugs has been demonstrated nicely by Leftwich.<sup>11</sup> He used the serum of patients receiving sulfonamide medication and obtained reactions (wheal and erythema) in twenty-eight of thirty patients who showed clinical evidence of sensitivity to these drugs. The best reactions were obtained with sera having a sulfonamide level of greater than 2 mg./100 c.c. and from patients who had received the drug for more than five days. Fink, Burton and Wheeler<sup>6</sup> failed when they applied this method in children with sulfonamide hypersensitivity.

The *passive transfer test* has proven most disappointing, even in the experimental drug allergies, when the nature of the sensitizing antigen is known.<sup>10</sup>

Walzer's technique of demonstrating indirectly the passive transfer of sensitivity by the oral administration of the antigen has not been extensively employed in the study of drug allergy. Lang and Der<sup>12</sup> report the use of this method in the experimental animal sensitized to quinine, iodine, and neoarsphenamine. Kenedy<sup>8</sup> was able to transfer hypersensitivity, passively, to phenolphthalein in man. He gave the drug twenty-four and four hours before the intradermal injection of serum obtained from a phenolphthalein-sensitive individual. This method is successful when the antibody titer is too low to be detected by the classic passive transfer. It might prove worth while in the study of drug allergy.

When large bullae are present, passive transfer tests might be attempted with fluid aspirated from these lesions. Mixtures of blister fluid and of the suspected drugs may prove valuable for direct skin tests.

Many years ago Oriol<sup>13</sup> succeeded in isolating an aspirin-proteose compound from the urine of a patient with allergic edema due to acetylsalicylic acid. This compound gave positive intradermal reactions, while both the pure drug and the proteose alone failed to do so.

## SUMMARY

The following techniques are available for the study of drug hypersensitivity:

1. *Tests using pure, unaltered drug as antigen.*
  - Patch test.
  - Intradermal test.
  - Tongue test.
  - Buccal mucous membrane test.
  - Conjunctival test.
  - Leukopenic test.
  - Readministration.
2. *Tests using combinations of drug and serum proteins.*
  - Drug and serum *in vitro*.
  - Drug and serum *in vivo*.
3. *Passive transfer tests.*
  - Prausnitz—Kuestner.
  - Oral antigen.
  - Intravenous antigen.
4. *Miscellaneous.*
  - Blister fluid.
  - Passive transfer.
  - Fluid and drug as antigen for intradermal test.
  - Use of other body fluids and exudates.

## CONCLUSION

This review of the mechanism of the production of drug allergy and of the methods available for its demonstration is intended to lessen the pessimism which surrounds this subject. This pessimism can be attributed largely, perhaps, to the failure of any one method of testing to prove valid in all of the many types of hypersensitivity produced by the myriad of drugs now in daily use. The greatest emphasis should be placed on the pathogenesis of the disorder in the individual patient. More or less standard techniques of study can then be applied at the strategic points which are most likely to be susceptible to testing. Such an approach will not always be successful. However, this should prove more valuable than a rigid adherence to one routine of testing, or a pessimistic abandonment of all forms of skin testing in cases of suspected drug sensitivity.

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# CHEMICAL INVESTIGATIONS OF GIANT RAGWEED POLLEN

## Part I

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THERE have been many attempts by various investigators to isolate in pure form, or at least to characterize chemically, the substances in pollens which are responsible for their allergenic activity. The excellent review of "Chemical Studies on the Allergens in Pollens" by Newell<sup>9</sup> summarized the work in the field to the year 1942, and the recent "Critical Review of the Literature of Pollen Allergens" by Wodehouse and Coca<sup>14</sup> has brought this summary further up to date. In view of the above-mentioned papers, only pertinent references will be cited hereafter.

The application to the study of pollen constituents of physicochemical methods, especially the use of the ultracentrifuge and the electrophoresis cell, has produced much valuable data. Abramson, Moore and Gettner<sup>1,2,3</sup> subjected an extract of ragweed pollen to electrophoretic separation in the Tiselius cell. They found a major unpigmented component of giant ragweed pollen to be present over a pH range of 3.5 to 7.5 without apparent dissociation, although the fraction showed two peaks at pH 3.5. A small quantity of the electrophoretically homogeneous component was isolated. It was named trifidin. By means of ultracentrifuge and diffusion measurements this group of investigators calculated the molecular weight of trifidin to be about 5,000. Trifidin diffused through cellophane, gave protein-like reactions and also a positive carbohydrate test. It produced an allergenic response in ragweed-sensitive patients. The quantity of material isolated by means of the Tiselius technique was of necessity small and for that reason more complete data on the chemical constitution of trifidin are lacking.

In an interesting paper by Rockwell,<sup>10</sup> a procedure was outlined for precipitating an active material from ragweed pollen extract by the simple addition of concentrated hydrochloric acid to the solution. The precipitate so formed was centrifuged, washed, dissolved, and reprecipitated several times. It was then dialyzed and dried at low temperatures in vacuo. From an elementary analysis of the material, Rockwell calculated its molecular weight to be about 4,500. A carbohydrate-content analysis and other data were used to substantiate this figure. The author proposed a flavonol-pentose-protein combination as the structure of the substance.

With the above evidence in mind it was decided to investigate further this relatively low molecular weight, protein-like ragweed-pollen component, with the view to isolating by other chemical means a sufficient

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quantity of the material to make it possible to establish more fully its chemical nature. In working out an isolation procedure, efforts were made to minimize adsorption effects, and at the same time to obtain as much information as possible about the chemical nature of the active compound. The following procedure was employed. An aqueous extract of giant ragweed pollen was dialyzed. The dialysate was subjected to a systematic elimination of various protein components by precipitation with easily removable precipitants. The method was based upon the studies of Hiller and Van Slyke<sup>8</sup> who showed, (1) that trichloroacetic acid precipitated proteins but left in solution "albuminoses" and "peptones," (2) that picric acid precipitated protein material down to the amino acid stage, and (3) that phosphotungstic acid precipitated proteins, polypeptides, peptides and even some of the amino acid (and some carbohydrate derivatives as well). It was hoped that by such a systematic study we would not only be enabled to characterize chemically the active material, but also to isolate it.

In order to obtain at least a rough comparative estimate of the allergenic potency of the various extracts and fractions which were isolated from the pollen, all extracts were adjusted so that their final volume would be the same, and then a sample of the solution was taken for testing purposes.

After being passed through a Seitz filter, the extracts were injected intradermally into ragweed-sensitive patients and the size of the wheal measured and recorded as 0 to ++++. A standard ragweed extract containing 0.01 mg. nitrogen per ml., called R 0.01, was injected at the same time for comparative purposes. Nonsensitive individuals were included as controls. The average of the wheal size (number of pluses) was the basis for comparison. When possible, ten to twenty patients were tested with each extract.

In order that we might further determine the specificity of the various fractions, passive transfer experiments by the method of Prausnitz and Kuestner were carried out.

#### EXTRACTION AND DIALYSIS

Four hundred and fifty grams of commercially available giant ragweed pollen were completely defatted with petroleum ether, dried in a current of purified air and then shaken with 3 liters of distilled water, and allowed to settle overnight in the refrigerator. The supernatant liquid was centrifuged and then filtered. Three more aqueous extractions of the pollen were performed in this manner.

The combined extracts were concentrated to about 400 ml. in an efficient vacuum still. A small amount of insoluble material settled out and was removed by filtration. Since the precipitate was found to be insoluble, even in 0.01 N sodium hydroxide, it was discarded.

After diluting the solution to 2 liters, a 500 ml. portion was dialyzed continuously for fourteen days within a piece of previously tested Visking



cellophane sausage-wrapping of 4 inches circumference. The remainder of the solution was similarly treated. Preliminary experiments indicated that fourteen days was the optimum time for the removal of the diffusible active material. The dialyzing apparatus employed was a modification of the vacuum dialyzing device of Hanke and Koessler,<sup>7</sup> and it has been previously described.<sup>11</sup>

TABLE I. RESULTS OF CHEMICAL TESTS PERFORMED  
ON EXTRACT 6 D

Biuret	—
Xanthoproteic	+
Picric Acid	++
Trichloroacetic Acid	+++
Phosphotungstic Acid	++++
Ninhydrin	++++
Molisch	+++
Benedict	++
Total Nitrogen	0.020 mg. per ml.

TABLE II. EFFECT OF HEAT ON SKIN  
REACTIVITY OF EXTRACT

	Skin Reactions Obtained with Dialysate Heated for One Hour to			Skin Reactions with R 0.01
	50° C	75° C	100° C	
Case 1	+++	+++	+++	+++
Case 2	++	+	+	+
Case 3	++	++	++	++
Case 4	++++	++++	++++	++++
Case 5	+++	++	+++	+++
Case 6	++	+	+	++
Case 7	+++	++++	++++	++
Case 8	+	+	+	+
Case 9	++	+	+	+
Case 10	+++	++	+++	+++
Case 11	+	0	+	++
Case 12	++	++	++	++
Case 13	+	+	+	+

The four portions of dialyzed extract were combined, evaporated in vacuo to a small volume and redialyzed. Much material precipitated within the cellophane sac and was preserved for other studies.

All dialysates were combined, evaporated in vacuo to 1 liter and redialyzed. These combined redialysates were evaporated in vacuo to 2 liters. A sample of this solution, labeled 6 D, was tested for activity and found to give approximately the same skin test reactivity as the standard R 0.01. Extract 6 D gave chemical tests listed in Table I.

A small sample of 6 D was immersed for one hour in a bath maintained at 100° C. and then cooled in ice water. A second and third sample were treated similarly; the temperatures maintained being 75° C. and 50° C., respectively. These samples were tested, along with R 0.01, on thirteen patients. Heating seemed to have a very small effect on the skin reactivity of this extract, as may be seen from the data in Table II.

Another small portion of 6 D was divided into two parts. One was

buffered at pH 4 and called 6 D 4; the other buffered at pH 8 and called 6 D 8. Both solutions were treated with an equal volume of a 1:1 mixture of butyl alcohol and chloroform and shaken in a shaking machine for three hours. The mixtures were then centrifuged. All organic solvents and any material which precipitated at the interface of the immiscible liquids were removed.

TABLE III. EXTRACT REACTIVITY  
AFTER REMOVING PROTEINS

Sample	Average Skin Reactivity (11 cases)
6 D	2.2+
6 D 4	1.8+
6 D 8	1.7+
R 0.01	2.3+

This treatment was repeated until there was no evidence of further precipitation on three successive shakings. All normal proteins should be removed by this procedure. After eliminating dissolved traces of the organic liquids the aqueous extracts were then tested for skin reactivity. The results are given in Table III. Although a small quantity of material from the dialysate 6 D was denatured and precipitated at the water-butyl alcohol-chloroform interface, no great loss in skin reactivity of the extract resulted.

#### TREATMENT WITH TRICHLORACETIC ACID

Into the 2 liters of 6 D a sufficient quantity of concentrated trichloroacetic acid solution was introduced so that the final concentration of the acid was 5 per cent. The mixture was allowed to stand overnight in a refrigerator. A small quantity of dark, finely divided material settled out. This was removed by filtration and discarded.

The clear yellowish-brown filtrate was extracted with ethyl ether in a continuous all-glass extractor. By renewing the ether daily, it required ten days to rid the pollen extract completely of the trichloroacetic acid. The resulting solution was brought to pH 7 by the addition of 20 per cent sodium hydroxide and then was evaporated in vacuo to 1 liter. The concentrate was again acidified with trichloroacetic acid, allowed to stand in the refrigerator for eighteen hours, filtered, extracted, and neutralized as described above. Finally water was added until the volume was 2 liters. The solution was designated 6 DT.

Eight ragweed-sensitive patients showed 6 DT to be as skin reactive as 6 D, which was comparable in activity to the standard R 0.01. Apparently little or no allergenic activity was removed by trichloroacetic acid. Inasmuch as the active material was not precipitated by trichloroacetic acid, it could not have been a true protein.

## TREATMENT WITH PICRIC ACID

To the 2 liters of 6 DT, one and one-half volumes of saturated picric acid solution were added. After standing in the refrigerator overnight, the material was centrifuged, yielding a clear yellow liquid and a small quantity of dirty yellow precipitate. The solid was discarded. The solution was neutralized, then evaporated in vacuo to about 1 liter. The pH of the liquid was adjusted to 2, and the picric acid was completely removed by ethyl ether in an all-glass continuous extractor. A current of purified air served to remove any dissolved ether from the resulting clear brown solution. Enough 20 per cent sodium hydroxide solution was added to bring the pH to 7. No change in color or clarity resulted.

The liquid was evaporated in vacuo to 500 ml. Again, it was treated with one and one-half volumes of saturated picric acid, allowed to stand for eighteen hours in the refrigerator, centrifuged, extracted, and neutralized as described above. This clear brown liquid, labeled 6 DTP, was diluted to 2 liters and a sample removed for testing.

There was no appreciable change in skin reactivity. Results on fifteen patients showed 6 DTP to be as skin reactive as the standard R 0.01. Apparently the picric acid treatment removed little or none of the active substance. It, therefore, could not have been an "albuminose" or "peptone."

## TREATMENT WITH PHOSPHOTUNGSTIC ACID

A solution containing 300 gm. of phosphotungstic acid and 180 ml. of concentrated hydrochloric acid was added to the 2 liters of 6 DTP. Under continuous stirring a heavy, non-homogeneous, greyish precipitate was formed. Standing overnight in the refrigerator resulted in a great increase in the amount of precipitate. The solids were filtered off and washed with ice-cold dilute acidified phosphotungstic acid solution. Inasmuch as some of the precipitate continually dissolved during the washing, the process was discontinued after 500 ml. of wash liquid was employed. The combined filtrate and wash liquids were labeled Y and set aside for subsequent study.

The phosphotungstate precipitate was suspended in water and extracted eight times in a large separatory funnel with 300 ml. portions of a 1:1 amyl alcohol and ethyl ether mixture. A small quantity of the precipitate failed to dissolve during this treatment, even upon further acidification; it was therefore removed and discarded. The solution was extracted twice more with 1:1 amyl alcohol-ether mixture, and then four times with ethyl ether. A current of purified air removed the residual ether from the solution. Testing with  $\text{BaCl}_2$  proved the absence of any phosphotungstic acid in the liquid. During the first few extractions considerable amounts of reddish-yellow coloring matter were removed. The resulting solution, named 6 DTPF, was clear and light-orange in color.

It was brought to pH 7 by the addition of 20 per cent sodium hydroxide. Water was added until its volume was 2 liters.

Clinical tests on twenty-three patients indicated that 6 DTPF was about two-thirds as skin reactive as the standard R 0.01. Inasmuch as this loss in activity might be partly accounted for by the phosphotungstate which dissolved on washing, it seemed expedient to test solution Y which contained this material.

TABLE IV. RESULTS OF CHEMICAL TESTS  
PERFORMED ON EXTRACT 6 DTPF

Xanthoproteic	Slight
Hopkins-Cole	Negative
Biuret	Slight (reddish)
Ninhydrin	+++
Molisch	+++
Benedict	Negative

The combined filtrates and washings, Y, were evaporated in vacuo to about 300 ml. The solids which precipitated during the concentration were removed by filtration, but were not washed. The filtrate was extracted with 1:1 amyl alcohol-ether mixture until free of phosphotungstate ion. It was then extracted with ethyl ether, dissolved traces of which were subsequently removed by a current of purified air. On neutralizing with 20 per cent sodium hydroxide, the yellow solution was diluted to 1 liter. A sample was taken for clinical testing.

Examination revealed that Y was about one-third as skin reactive as R 0.01. This represented the one-third loss of skin reactivity of 6 DTPF as compared with 6 DTP which gave the same skin reaction as R 0.01. It would therefore appear that the active component is precipitable by phosphotungstic acid.

In an endeavor to purify the material still further, 15 ml. portions of 6 DTPF were shaken with varying quantities of well-washed Norite A. This accomplished the removal of color from the solution. The resulting filtrates varied from the original reddish-yellow to colorless as the quantity of added Norite was increased. However, skin tests with these filtrates showed an almost total lack of allergenic activity. Subsequent testing of the original 6 DTPF, which had been kept in the refrigerator for thirty days while the above operations were being performed, also registered a total loss of allergenic activity. The reason for this is thus far unknown.

The loss of activity of the extracts at this stage of the work was disappointing, especially since it still leaves in doubt the answer to the question of whether Norite A will remove the color alone or the color plus the activity of this fraction.<sup>4,5,12</sup> While we are repeating and continuing these studies, the results obtained so far seemed to warrant their publication at this time. Chemical tests made on 6 DTPF just prior to the inactivation are listed in Table IV.

## DISCUSSION

The investigations above described provide additional evidence that there is present in an aqueous extract of giant ragweed pollen an allergenically active substance that dialyzes through cellophane membranes. Only half of the original allergenic activity could be transferred to the dialysate, even after fourteen days of continuous dialysis with a constant flow of water past the cellophane bag. This finding, coupled with the fact that the fraction which did not diffuse through the dialyzing membrane retained about half of the total activity, constitutes additional evidence for the hypothesis of multiple allergens in pollen extracts.

The fact that the active substance in the dialysate is heat-stable, is not denatured at an interface, is not precipitated by trichloroacetic acid nor by picric acid, constitutes proof that it is not a protein in any strict sense of the word—nor is it an “albuminose” or “peptone.” Yet the extract yielded qualitative tests for protein groupings as well as for carbohydrates. Phosphotungstic acid did precipitate the allergenically active substance in the dialysate of the pollen extract. This reagent will precipitate peptide-linked compounds of a large range in molecular weight. It will also precipitate some of the amino acids, as well as some of the carbohydrate derivatives. It would appear, therefore, that the active material in the extract dialysate under study was a comparatively low-molecular-weight peptide or carbohydrate, a mixture of the two, or perhaps a nitrogen-containing carbohydrate.

The physical and chemical properties of the material confirm this. Only a comparatively low-molecular-weight compound would dialyze through cellophane. The strong ninhydrin test, given by the extract after the last stage of purification, indicated the presence of amino groups, while the pinkish biuret test indicated a small peptide-linked molecule. However, the strongly positive Molisch test was evidence of the presence of a carbohydrate.

In the last stage of purification the extract was of a light orange color. This color could be removed by Norite A, but with the unfortunate loss of activity at this stage, it was not possible to prove whether or not the loss of color was accompanied by loss of activity.

The method of purification in these investigations differed so drastically from that employed in other researches<sup>6,10,13</sup> on the subject that comparisons are difficult to make. It is hoped, that upon repeating and continuing these experiments, sufficient data will be collected to determine whether or not the active principle in our final fraction is trifidin.

## SUMMARY

1. An aqueous extract of defatted giant ragweed pollen was exhaustively dialyzed, about one-half of its allergenic activity appearing in the dialysate.

2. The active principle in the dialysate was heat-stable and not denatured at an interface.

3. The dialysate was further purified by treatment with trichloroacetic acid. After the removal of that precipitant, saturated picric acid was added, and then the excess eliminated. Neither treatment precipitated the active principle nor was the skin reactivity of the extract appreciably changed.

4. Phosphotungstic acid precipitated the active principle. Upon adding the insoluble addition compound of the phosphotungstic acid, thereby making it soluble again, the activity was recovered.

5. The most highly purified fraction yielded a positive ninhydrin, biuret and Molisch test.

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# THE APPLICATION OF A TISSUE CULTURE TECHNIQUE IN THE CLINICAL EVALUATION OF BACTERAL HYPERSENSITIVITY

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THE role of bacterial hypersensitivity in various diseased states has been the subject of many reports in the literature. The subject has been reviewed by Rich<sup>5</sup> and Scherago.<sup>8</sup> How extensive a role this phenomenon may play in human disease awaits the development of a more reliable clinical method of testing for hypersensitivity than those methods currently available. The only practical method to date of testing patients for bacterial allergy is by the skin test method. The criticisms of the skin test are many. It is not a sensitive test, in that many apparently normal patients exhibit considerable skin reactivity.<sup>4</sup> It does not lend itself to the quantitative determination of hypersensitivity. The anaphylactic reaction cannot be avoided. The number of tests that can be performed is always limited, and the test is not without danger. Therefore, the tissue culture technique was explored as a possibility for developing a more reliable clinical method for determining the presence of bacterial hypersensitivity.

The use of tissue cultures in the study of bacterial hypersensitivity is based upon the fact that the cells of the body with bacterial hypersensitivity are killed *in vitro* by contact with the specific bacterial protein, whereas such cells from the body with anaphylactic, Arthus or pollen-type sensitivity are not killed *in vitro* by contact with the specific protein.<sup>6</sup>

## METHODS AND MATERIALS

*Bacterial Antigens.*—Unless otherwise noted, the antigens employed in these tests were bacterial filtrates prepared from twenty-four-hour broth cultures. Various species of bacteria maintained on blood agar were subinoculated into broth tubes and incubated at 37° C for twenty-four hours. At the end of this time the culture was centrifuged and the clear supernatant fluid put through a Seitz filter. Appropriate sterility tests were performed as a check on the filtrate. Dilutions of the filtrate were prepared in physiological saline solution.

*Preparation of the Buffy Coat.*—Nine cubic centimeters of freshly drawn blood were immediately added to 1 c.c. of a 2 per cent sodium citrate solution and then centrifuged. The plasma was removed and the buffy coat coagulated by the addition of calcium Ringer's solution. The buffy coat was easily separated from most of the red cells by repeatedly teasing the red cell strands and washing with Ringer's solution. The buffy coat was kept in Ringer's solution until used.

*Method of Performing the Test.*—The buffy coat was placed on a large black rubber stopper and explants were prepared using a 1.5 mm. corneo-

## BACTERIAL HYPERSENSITIVITY—NANTZ AND BLATT

TABLE I. PATIENTS SHOWING TITERS OF 1:1000 OR HIGHER AGAINST VARIOUS ANTIGENS

Patient	Antigen	Titer†	Clinical Diagnosis
GD	H-Streptococcus Gr-Streptococcus	1:10,000 1:5,000	Rheumatoid arthritis—1 year Bilateral uveitis—6 months
GB	Staphylococcus aureus	1:10,000	Asthma—5 years
TO	H-Streptococcus H-Staphylococcus Gr-Streptococcus	1:5,000 1:10,000 1:5,000	Rheumatoid arthritis—20 years
SK	H-Streptococcus, pneumococcus mixed vaccine* Pneumococcus Type I	1:5,000 1:1,000	Recurrent keratitis, bilateral— 10 years

† Highest dilution of antigen showing suppression of cells.

\* Antigen supplied by Dr. Leslie Gay, Johns Hopkins Hospital.

scleral trephine. With this method as many as forty explants were rapidly prepared from one buffy coat. Each explant was placed on a separate cover glass and two drops of the bacterial filtrate were dropped directly on the explant. One drop of concentrated fibrinogen and one drop of full strength thrombin were added. As soon as the explants coagulated, the cover glasses were inverted over hanging drop slides containing Ringer's solution and ringed with vaseline. The slides were placed in a moist chamber and incubated at 37° C.

Normally the small wandering cells begin to migrate in a few hours. At twelve hours migration ceases and the cells then remain stationary and viable for periods up to four days. When migration has ceased the hundreds of cells form a dense corona around the explant with many cells scattered throughout the media. This degree of extensive cell migration was arbitrarily recorded as 4. If there are only a few scattered viable cells along the edge of the explant the test is recorded as 1. Explants surrounded by viable cells in limited numbers are recorded as 2. Designations 3 and 4 refer to the normal picture of extensive cell migration with corona formation. If the explant is completely necrotic it is recorded as 0.

## EXPERIMENTAL

This report concerns itself with the results of the first fifty patients tested against the filtrates from the following bacteria: Streptococcus hemolyticus group A, Streptococcus viridans, Staphylococcus aureus hemolyticus, Staphylococcus aureus anhemolyticus, and Diplococcus pneumoniae. Forty of the patients tested showed no suppression to any of the antigens even in full strength. Six showed suppression to some of the antigens either in full strength or in dilutions of up to 1:100 while the remaining four patients all showed suppression in dilutions from 1:1,000 to 1:10,000 (Table I). These last four patients were all seriously ill and included the only two patients with rheumatoid arthritis tested thus far.

The slide cultures were retained for three days, but positive results



# BACTERIAL HYPERSENSITIVITY—NANTZ AND BLATT

TABLE II. PATIENT (SK) TITERED TO H-STREPTOCOCCUS  
PNEUMOCOCCUS MIXED VACCINE

Antigen	Dilution	10 Hours	36 Hours	45 Hours	60 Hours
H-Streptococcus, pneumococcus mixed vaccine	1:1,000	1	0	0	0
	1:5,000	2	1	0	0
	1:10,000	3	3	3	3
	1:50,000	4	4	4	4
	1:100,000	4	4	4	4
Control	Ringer's	4	4	4	4

TABLE III. EFFECT OF DESENSITIZATION UPON THE  
HYPERSENSITIVITY TITER (PATIENT GD)

Antigen Dilution	Before Desensitization	After Two Months Desensitization
H-Streptococcus 1:100	0	0
1:1,000	0	2
1:5,000	0	4
1:10,000	1	4
1:50,000	4	4

could be read as early as ten hours. Occasionally when performing a titration it became necessary to keep slides for forty-eight hours. In such cases where a 1:1,000 dilution showed complete suppression and a 1:10,000 dilution no suppression, the dilution of 1:5,000 showed no change until twenty-four hours when the cells clumped and rapidly underwent necrosis. The final titer was recorded as 1:5,000 (Table II).

When specific hypersensitivity is determined, the patient may then be desensitized and subsequently retested. Desensitization may be continued until the titer level is sufficiently low and, in addition, the patient may be tested from time to time to note any return of the hypersensitive state. Table III demonstrates this value of the test. This patient had rheumatoid arthritis with recurrent uveitis in both eyes. The titer level before desensitization was 1:10,000; at the end of two months of desensitization it had dropped to 1:1,000. Although symptom-free at the present time, the patient shows a titer of 1:5,000 against a green streptococcus. As more antigens become available new tests will be performed with a view to preparing additional antigens for desensitization purposes.

## DISCUSSION

The use of tissue cultures in the study of bacterial hypersensitivity is not new. Holst<sup>2</sup> in 1922 was the first who attempted to demonstrate a specific tissue hypersensitivity to tuberculin in the experimental animal. His failure may be attributed to his methods. Rich and Lewis,<sup>7</sup> however, in 1928 succeeded in demonstrating a specific toxic effect of tuberculin in high dilutions on both the splenic cells and the white cells of the buffy coat of tuberculin-sensitized guinea pigs. This reaction was entirely absent

in normal animals. These results have since been confirmed by Aronson<sup>1</sup> and Moen and Swift.<sup>3</sup> Moen was able to demonstrate the same specific necrosis of tissue cultures taken from animals sensitized to group C streptococci only when these cells were mixed with the specific antigen and not with other related strains. This effect was observed when the streptococcic antigen was diluted even to 1:6,000. Moen used splenic explants and read the test at the end of four days by comparing the rate of growth of the explant in the bacterial antigen with the rate of growth of the control. This ratio was referred to as the cytotoxic index and was invariably less than 1 in hypersensitivity and 1 or larger in normals. In attempting to correlate the results of his tests with the skin test, Moen observed that "no correlation was found between the degree of cutaneous reactivity to a given bacterial extract and the degree of sensitivity of splenic explant cells to the same extract *in vitro*."

There are two serious criticisms of the test as performed by these investigators. First, the explants do not remain viable and the cells do not migrate in the absence of plasma. Unfortunately plasma contains many properties which can interfere seriously with the sensitivity of the test. Moen states "other tissue culture studies on hemolytic streptococcic allergy indicate that immune plasma has a neutralizing effect on the toxic action of streptococcic extract when tested on sensitive cells." Consequently Rich found it necessary to combine allergic cells plus allergic plasma, allergic cells plus normal plasma, and normal cells plus allergic plasma in order to evaluate properly each individual test. This difficulty has been overcome here by the substitution of fibrin for plasma. In this fibrin matrix the small wandering cells migrate as well as in plasma. Furthermore we are not dealing with plasma precipitins and agglutinins which interfere seriously with the test. Finally, the necessity of keeping explants for four days and measuring cytotoxic indices makes the test rather cumbersome. Each test must be controlled with a separate tissue culture, and the readings are rather tedious. We found that explants placed on a hanging drop slide filled with fluid showed better cell migration than explants placed in tissue culture slides containing an air chamber. It therefore became unnecessary to make cytotoxic index determinations. The test can be read by merely a quick glance at the low power magnification. With these modifications we have found it possible to make as many as forty separate tests from a single 9 c.c. specimen of blood. The patient may thus be tested separately to many antigens or accurately titrated by using various dilutions of a single antigen.

#### SUMMARY

Tissue culture of the patient's white blood cells in the presence of bacterial filtrates is offered as a new clinical test for bacterial hypersensitivity.

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## ACTIVE SENSITIZATION TO POLLEN

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IN the course of a series of local passive transfer tests four recipients have become skin sensitive to ragweed pollen. These are four of forty-seven who served for experiments with ragweed. Only ragweed sensitizations have developed, in spite of the fact that a larger number of experiments have been done with other highly antigenic pollens such as timothy, sagebrush, pigweed and mountain cedar, involving the services of 123 recipients in all. None of the four who developed sensitization to ragweed did so to other pollens, though their exposure to them in these experiments was as great or greater.

The recipients were random volunteers selected only for their firm responsive skins and histories of freedom from pollen sensitizations. But, in common with the entire population of the community, all had suffered heavy seasonal exposure to the pollen of ragweed, and to a lesser extent to that of timothy and related grasses, in most cases for their entire lives. But none had at any time previously been exposed to the other pollens used in the experiments. It was noted that in the ragweed tests the recipients responded with irregularities which did not occur in the tests with the pollens to which they had never been exposed. A large proportion of them accepted passive transfer to ragweed-sensitive serum very poorly and several failed completely, though accepting transfer to other pollens readily enough, which suggests the presence of a blocking antibody. One reacted to the ragweed reaginic serum, leaving the sites thereafter negative to ragweed, indicating the presence of circulating ragweed antigen. Thus there is evidence that a large proportion of a population annually exposed to ragweed pollen respond to the pollen in other ways than by developing clinical sensitization to it.

### CASE REPORTS

*Case 1.*—A woman, aged twenty-seven, gave a personal history of no allergy, except of having had hives when very young. This was believed to have been due to fish and citrus fruits though not demonstrated by skin tests. Now she eats these and all other foods without symptoms. She has no immediate family history of allergy but her brother's child has eczema from wheat and cow's milk.

She was shown by scratch test to be skin negative to ragweed, sagebrush, mountain cedar, timothy, and pigweed. Before she served in ragweed tests she had already served in experiments with sagebrush, mountain cedar and timothy, accepting passive transfer and responding normally in every way.

On September 24, 1946, she was used in a ragweed neutralization experiment receiving in all 14.3 units\* of ragweed. She was proved negative to ragweed at this time by seven negative retests.

On November 19, 1946, she was again used in a ragweed neutralization experiment. At this time she was not suspected of being sensitive to ragweed but it was noticed that the transfer sites were not neutralized by the amount of ragweed

\*One unit = 0.00001 mg. N.

(.0746 units) which was known to be well beyond the neutralizing potency for the serum with other recipients. It is, therefore, probable that she had some sensitization to ragweed at this time. The experiment required the injection of a total of 121 units.

On January 11, 1947, she again served in a ragweed neutralization experiment. This time she reacted to the control, 0.01 c.c. of ragweed, 1,000 units per c.c. with a wheal 5 mm. and erythema 20 mm. in diameter. Since this reaction was small and it was thought to have been influenced by strongly reacting transfer sites on the same arm, it was not interpreted as sensitization at the time. She was, however, tested again on June 3, 1947, when it was found that she gave a similar reaction of 5 and 15 mm. to 0.01 c.c. of 100-unit ragweed. This confirmed the former test on January 11.

It is uncertain whether this recipient acquired sensitization before or after November 19, 1946. If the former, it followed the injection of 14.3 units with a time lapse of less than two months; if the latter, it followed the injection of 135.3 units with a time lapse of less than four months. In either case the dosage seems strikingly small considering that an immunizing course of treatment with ragweed pollen calls for the injection of 11,680 units. The dosage value of 14.3 units is less than the third dose in the treatment series, and 135.3 is less than the seventh.

*Case 2.*—A woman, aged twenty-two, has mild symptoms resembling hay fever from June to September, especially in July and August. At other times is easily made to sneeze by smoke and dust. She was shown by scratch test to be negative to ragweed, pigweed, timothy and mountain cedar, but gave marked reactions to cat hair and house dust, and a border-line reaction to mixed feathers. Before she was used in ragweed experiments she had been used in timothy and Bermuda-grass experiments, and behaved normally in every way.

On September 5, 1946, she was used in a ragweed *in vivo* neutralization experiment. At this time she was shown to be nonsensitive by ten negative retests with 0.01 c.c. of ragweed, 100 units per c.c. In this experiment she received a total of 18 units of ragweed.

On October 31 she was again used for a similar ragweed experiment. In this, all but one of the retests with 1,000-unit ragweed were positive, while in an identical check experiment done on another recipient, all retests were negative except the unneutralized controls. Her sensitization was confirmed on June 3, 1947, when she responded to 0.01 c.c. of ragweed, 100 units per c.c., with a wheal of 8 and erythema of 40 mm. diameter. It would thus appear that this recipient became sensitized in two months or less after the injection of only 18 units of ragweed pollen or slightly more than the equivalent of the first two doses of the ordinary treatment schedule.

*Case 3.*—A woman, aged thirty-nine, has dermatographia and gave a personal history of having had a severe attack of hives at the age of sixteen from eating soft-shell crabs, and again in her early thirties from the same cause. She can eat canned crabmeat and all other sea food with impunity. Her antecedent family history is negative but her one son is frankly allergic. At the age of seven to eight months he had eczema from eggs, shortly followed by asthma from the same cause. Later he developed hay fever and asthma from ragweed pollen.

The mother was shown to be negative to ragweed by scratch test. Before serving in ragweed experiments, she had been used in a timothy and a Bermuda grass experiment and responded normally.

On July 30, 1946, she served in a cross neutralization experiment, receiving a total of 36 units of ragweed. At this time she was shown to be negative to ragweed since all the ragweed reciprocals were negative.

On October 29, 1946, she served in a ragweed *in vitro* neutralization experiment. At this time she reacted to all the retests, though a substantial proportion of these should have been completely neutralized. Her sensitization was confirmed at a later date (December 17, 1946) when it was found that 0.01 c.c. of 1,000-unit ragweed endermally at a normal site produced a wheal of 11 mm. diameter and erythema of 25 mm. It thus appears that this recipient became sensitized after the injection of 36 units of ragweed, and after not more than three months.

*Case 4.*—A man, aged thirty-two, gave no personal history of allergy, except that working with guinea pigs caused a rash on his hands and arms which was thought to be contact dermatitis from the fur of the animals. However, both scratch and patch tests with guinea pig fur, and likewise with their food and bedding materials, proved negative. During the course of the experiments he was discovered to be skin sensitive to timothy, 0.01 c.c. of 1-unit pollen extract endermally producing a wheal of 9 mm. and erythema of 50 mm. diameter.

His family history shows that his father suffered severe asthma during the late summer months.

The man was shown to be negative by skin test to sagebrush, mountain cedar and ragweed, so was considered a suitable recipient for experiments with these antigens.

On October 18, 1945, he served in a ragweed neutralization experiment. The control tests showed that he was negative to ragweed at this time. He received a total of 12 units in this experiment.

On March 15, 1946, he served again in a ragweed *in vivo* neutralization test, receiving a total of 120 units of ragweed pollen. The retests showed him to be negative to ragweed at this time.

On September 5, 1946, he served in a tall and short ragweed neutralization experiment, receiving 48 units of ragweed in all. Retests and reciprocal tests were negative, proving him to be nonsensitive to ragweed at this time.

On November 4, 1946, he was used again in a ragweed *in vitro* neutralization experiment, receiving a total of 125 units. The retests in this experiment failed to detect any appreciable amount of neutralization indicating that the recipient was strongly sensitive to ragweed. His sensitization was not recognized at the time but was subsequently brought to attention January 8, 1947, when it was found that 0.01 c.c. of 1,250-unit ragweed gave a reaction of 10 and 45 mm. in a normal site. It is apparent that this recipient became skin sensitive following the injection of 180 units of ragweed, between September 5 and November 4, 1946, about one year after his first and two months after his last ragweed injection.

At the close of the 1947 ragweed season all four persons reported having experienced no symptoms of hay fever though they had spent the entire time in regions infested with ragweed.

On September 16 all were tested again with ragweed for skin sensitivity, using 0.01 c.c. of short ragweed, 100 standard N. units per c.c. intracutaneously. Case 1 gave a wheal of 7 and erythema of 30 mm. in diameter; Case 2, 7 and 30 mm.; Case 3, 8 and 30 mm.; Case 4, 6 and 25 mm. Case 1 shows a definite increase in sensitivity from a reaction of 5 and 15 mm. to 7 and 30 mm. from the same dose, three months earlier. Case 2 shows a slight decrease from 8 and 40 mm. to 7 and 30 mm. from the same dose three months earlier. In Case 3 and Case 4 it is not known whether the final reactions of 8 and 30 mm. and 6 and 25

mm., respectively, indicate any change in sensitivity, since their earlier doses were much larger. The reactions of 11 and 25 mm., and 10 and 45 mm., respectively, which were obtained nine months earlier were elicited by 0.01 c.c. of ragweed of 1,000 and 1,250 units per c.c., amounts which we did not feel justified in using with cases of known sensitivity. It is probable, however, that Case 4, at least, has lost some sensitization.

It is well known that the serum used in local passive transfer tests is sometimes sufficient to induce a general skin sensitization. It is hardly possible that such could have been the case with these sensitizations because of the minute quantities of sera that were used. In all, Case 1 received 0.126 c.c.; Case 2, 0.5 c.c.; Case 3, 0.09 c.c.; Case 4, 0.41 c.c. of ragweed sensitive serum. Moreover, these sensitizations have persisted for from three to nine months, whereas passive sensitizations, even those resulting from transfusions of large quantities of blood, persist but a few weeks. It is therefore inescapable that these four recipients were actively sensitized by the injection of ragweed pollen extract.

Human beings are easily sensitized by injection to certain substances such as horse serum and some of the newer drugs but to most substances which are the causes of the ordinary allergies, sensitization can be accomplished only with the greatest of difficulty or not at all. Moreover, apparently only atopic individuals respond in this way. Thus Brunner<sup>1</sup> (1934) attempted to sensitize fifteen people using orris root, rabbit epithelium, egg, ascaris and cat dander. Only with orris and ascaris was he successful. Orris sensitization was one out of eight attempted; ascaris was three out of five.

He concludes that it is very difficult to sensitize human beings actively by subcutaneous injections of atopens which are common and important offenders. Those who were sensitized were inherently allergic to some other substance before the attempt was made. Though people with negative personal and family histories of atopy were included in the experiment, none of them became sensitized. The sensitizations thus artificially produced contrasted sharply with spontaneous sensitizations in that they were only transitory, disappearing in from one to two years.

A perusal of the literature has failed to reveal any report of human beings becoming sensitized to pollen through injection. On the contrary, many statements are found to the effect that such is impossible. Lamson and Miller<sup>5</sup> (1927) put the question to a searching test. They treated, by the usual course of therapeutic injections, thirty-three allergic patients with pollens to which they were nearly or quite negative. The only indication of sensitization which they encountered was that, "There are four instances, representing four different pollens and three patients, in whom the test two weeks after treatment was considered to be more positive than before treatment, but in no case has this been shown to be the case at the last test." They conclude that, "The injection of the amount of pollen that is commonly used for treatment . . . fails to induce positive

skin reactions in allergic patients who previously have given negative skin reactions to the pollen."

These authors argue that, though a positive skin reaction to pollen or other allergen is obtained after a patient has given consistently negative reactions for a month or more, this must not be considered proof that that particular sensitization has been recently acquired. It appears, they say, that this phenomenon might be explained by assuming that the sensitization had existed for some time, but that the threshold of resistance had but recently been exceeded.

One of the principal factors in spontaneous pollen sensitization is that of time; generally years. Thus it is that in Bermuda, where the only hay fever is caused by the pollen of Bermuda cedar, Hodgson<sup>4</sup> (1935) tells us that it affects only permanent residents; no case has ever been recorded among the many transients. The latter are gone again before they have time to develop sensitization. Phillips<sup>7,8</sup> (1928, 1932) records that persons sensitive to eastern grass settling in Arizona are nearly always free from hay fever for three to five years before they have time to succumb to the effects of the pollen of Bermuda grass which is known to be antigenically different from that of the eastern grasses. The same author<sup>9</sup> (1939) finds that, "Two years of seasonal contact seem to have been the time required to develop clinical evidence of sensitivity to the newly encountered pollen [beet] . . . with an adequate exposure in the third year." With regard to Johnson grass smut, Phillips<sup>10</sup> (1940) finds that it takes at least five years of exposure before the development of positive reactions.

It appears that the time factor may be influenced to some extent by the degree of exposure. Thus Nelson<sup>6</sup> (1934) studying the onset of hay fever by age classes records that it takes at least a number of years of exposure to pollen to develop sensitization. But he found that a preponderance of males became sensitized during the first decade of life, while with females it was during the second and third decade because, he says, the life of a small boy leads him among pollen-producing weeds much more than that of a small girl, the greater exposure of the former causing earlier development of sensitization.

Clark and Leopold<sup>2</sup> (1940) added to these observations of Nelson, their findings on European-born immigrants in relation to ragweed. Coming to America from countries where ragweed is virtually absent, these immigrants require the same exposure period to ragweed pollen as native Americans. They find that immigrants develop hay fever mostly after eleven to twenty years of exposure regardless of their age upon arrival, while native Americans develop it mostly at the ages of eleven to twenty in the same environment.

Figley and Elrod<sup>3</sup> (1928) reported the development of asthma from castor bean dust emanating from an oil mill, among the local population of Toledo. Of these people the authors say, "None of them had asthma

before moving into this district, and the onset of attacks varied from one to seventeen years after moving into the neighborhood." Thirty patients presented themselves for study. It was found that three became sensitized during the first year of their exposure, but the majority took two to five years. Only thirteen of the thirty persons showed personal or family history of atopy. However, since this is a larger proportion than would be found among a similar group of normal individuals, the authors feel justified in saying, "We feel that our series of cases helps to support the view that asthma occurs only in persons who are hypersensitive through inheritance," attributing the discrepancy in figures to the difficulty of getting adequate histories from people of so low a social standing.

Of the four cases with which the present report is concerned three became sensitized in much less than a year and one in about a year. All had a family or personal history of atopy. Only sensitizations to ragweed developed, though there was greater opportunity for sensitization to other pollens. This latter fact and the extremely short time taken for their sensitization are evidence that all were on the road to sensitization from their natural exposure to ragweed pollen, and that the injections of the pollen served only to accomplish the last step.

The problem requires further study before definite conclusions can be drawn. However, the evidence here presented points to the conclusion that, though it is extremely difficult to sensitize human beings to pollen by injection, it can be done providing they are inherently atopic and the pollen used is one to which they are annually exposed. And the corollary to this is: for making passive transfer tests only nonatopic individuals should be used, in so far as this can be determined, and they should be drawn from a population not regularly exposed to the antigens to be tested.

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# THE EFFECT OF DRUGS IN MODIFYING THE RESPONSE OF ASTHMATIC SUBJECTS TO INHALATION OF POLLEN EXTRACTS AS DETERMINED BY VITAL CAPACITY MEASUREMENTS

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A REDUCTION in vital capacity may follow the inhalation of aerosolized extracts of pollen in certain asthmatic subjects.<sup>6</sup> As Brown, et al<sup>1</sup> have also shown, reductions in vital capacity may occur in individuals with hay fever and bronchial asthma during the pollen season. The changes in vital capacity induced by us are reproducible, and the tests need cause little or no discomfort to the subject. The symptoms and signs which may accompany the pulmonary reaction resemble naturally occurring asthma in every respect except that they are usually of short duration. If necessary, the symptoms can be relieved and the vital capacity quickly increased by the administration of a suitable drug.

The three subjects chosen for these studies exhibited high degrees of responsiveness as indicated by marked reductions in vital capacity following exposure to aerosolized pollen extracts. Not more than a single exposure to a pollen to which the patient was sensitive was made on any one day, and the subjects were not tested during periods of spontaneously occurring asthma. With the subject seated and rested, exposure was carried out by a number of deep oral inhalations from a No. 40 DeVilbiss nebulizer supplied with oxygen flowing at a rate of 6 liters per minute. Vital capacity measurements were made with a Benedict-Roth metabolism machine arranged so as to produce a tracing of the expiratory curve on a moving drum.

Pollen extracts were prepared in the proportion of 1 gm. of dry pollen to 30 ml. of extracting fluid. Tests were also made using aerosolized solutions containing histamine in a concentration of 50 mg./ml. and acetyl-beta-methyl choline also in a concentration of 50 mg./ml. No fall in vital capacity occurred in control tests done with extracting fluid alone. The subjects were observed for signs of asthma during the tests and notes were made of their subjective sensations.

The capacity of four drugs to prevent the fall in vital capacity which regularly followed five inhalations of an aerosolized extract of birch pollen was investigated. The drugs used were aminophylline given intravenously in a dose of 0.48 gm., epinephrine given subcutaneously in doses of 0.3 ml. to 0.5 ml., atropine given intravenously in doses of 0.6 mg. and 1.2 mg., and pyribenzamine given intravenously in a dose of 25 mg. Of these agents, given in the manner described, aminophylline pro-

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vided the greatest protection to the patient, both with regard to fall in vital capacity and symptoms. Epinephrine gave definite but incomplete protection whereas neither atropine nor pyribenzamine afforded any protection whatsoever. The position of pyribenzamine in the treatment of asthma is still unclear, but there is a general agreement that this drug rarely gives prompt relief of the asthmatic attack. Atropine likewise is usually ineffective. These results, therefore, are in keeping with clinical experience and indicate that this method of investigation may provide a useful means of assaying the effectiveness of new drugs for the treatment of asthma.

Another series of tests were carried out to determine whether the vital capacity, once reduced as a result of inhalation of a pollen extract, could be restored by the administration of various drugs. It was found again that aminophylline was superior to the other drugs in this respect. Epinephrine given subcutaneously in doses of 0.3 ml. and 0.5 ml. was likewise effective but less so than aminophylline. A number of tests were done with Isuprel\* (1-(3<sup>1</sup>, 4<sup>1</sup>-Dihydroxyphenyl)-2-isopropylamino ethanol) in a concentration of 0.5 per cent. This was administered with the nebulizer in the same manner as the pollen extracts. Five deep inhalations of this solution was usually sufficient to increase the vital capacity markedly when this had been lowered by inhalation of a pollen extract. This preparation, administered in this manner, was more effective than subcutaneously administered epinephrine in the dosage used, but less effective than intravenously administered aminophylline. Atropine and pyribenzamine, both of which were given intravenously, were entirely without effect in restoring the vital capacity after this had been decreased by inhalation of pollen extract.

Tests were performed to determine the effect of pyribenzamine or atropine in preventing or relieving the reduction in vital capacity which could be readily produced in our subjects by exposure to aerosolized solutions of histamine or acetyl-beta-methyl choline (Mecholyl). The tests were similar to those described by Curry<sup>2,4</sup> and Curry and Lowell<sup>5</sup> in which histamine and Mecholyl were given parenterally. It was readily shown that atropine decreased the response to inhaled Mecholyl but pyribenzamine was without effect. In contrast to the results in the pollen tests, pyribenzamine gave complete protection against inhaled histamine and also restored the vital capacity when this had been lowered by inhalation of histamine. This result indicates in all probability that the failure of pyribenzamine to protect the subjects against the effects of inhaled pollen extracts was not due to the manner or dosage in which it was administered, and provides an argument against the hypothesis that histamine release is a determining factor in the production of the pollen-induced asthmatic attack.

\*Supplied by courtesy of Frederick Stearns and Co.

## SUMMARY

Measurement of changes in vital capacity was used as a means of studying the effect of various drugs in modifying the response of three asthmatic individuals to the inhalation of aerosolized pollen extracts, and to solutions of histamine and acetyl-beta-methyl choline. The results indicate that the method is a useful one for the study of bronchial asthma. The failure of atropine and pyribenzamine to influence the pulmonary response to inhaled extracts of pollens suggests that neither acetylcholine nor histamine are determining factors in the production of the pollen-induced asthmatic attack.

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## SUSPECTED DRUG SENSITIVITY

(Continued from Page 545)

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# Reports in Brief

Papers appearing in this section were read by title at the Third Annual Session, American College of Allergists, held in Atlantic City, June 6-8, 1947.

## FAILURE OF CERTAIN HISTAMINE-LIKE SUBSTANCES TO PRODUCE OR TO INHIBIT WHEELS IN THE HUMAN SKIN

### Preliminary Report

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PRIOR to 1942 experiments were performed with Dr. R. K. Lambert and with Dr. H. T. Clarke on the pharmacology of histamine-like substances on the eye and skin of man. Table I briefly summarizes the data available. In the intradermal tests mixtures were made and injected together intradermally. The volume of the injected material was between 0.03 and 0.05 c.c. In the eye, the inhibiting substance was permitted to act for several minutes before the histamine was introduced. Pertinent references on the general problem of the relationship on the spatial configuration of histamine-like substances to the problem are appended.

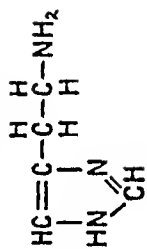
Of particular interest is the fact that imidazole methylamine does not produce a wheal in high concentration. Nor does it protect against intravenous histamine. More important, perhaps, would be similar studies with imidazole propylamine. Many of the compounds listed in Table I produce whealing due to irritation if they are not brought to pH 7.4. It was most surprising to see that 1 per cent ethylamine brought to pH 7.4 may be safely put into the eye without irritation. The reported wheal production by histidine was not observed in a suitably buffered solution. Evidently many histamine-like substances, especially imidazole, methyl imidazole and imidazole methylamine (protohistamine), neither reproduce the whealing response of histamine in the human skin nor do they readily inhibit the histamine reaction. Findings contrary to those reported here for histidine, allantoin and urea are in the literature.

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This research was supported in part by a grant from the Josiah Macy, Jr., Foundation. From the First Medical Service and the Laboratories of the Mt. Sinai Hospital, New York City.

TABLE I. FORMULA FOR HISTAMINE



	Compound or Mixture	Name	Conc.	Tissue	* Histamine-like Reaction	Inhibition of Histamine
1.	$\begin{array}{c} \text{H} \quad \text{H} \\   \quad   \\ \text{H}-\text{C}-\text{C}-\text{NH}_2 \\   \quad   \\ \text{H} \quad \text{H} \end{array}$	Ethyl amine phosphate (pH 7.4)	1.0% 0.1%	Eye Intradermal	None None	None of 1:1,000 None of 1:50,000
2.	$\text{HN}=\text{C} \cdot (\text{NH}_2)_2$	Guanidine	1.0%	Intradermal	None	None of 1:1,000,000 Histamine
3.	$\begin{array}{c} \text{HC}=\text{C} \\   \quad   \\ \text{HN} \quad \text{N} \\ \diagup \quad \diagdown \\ \text{CH} \end{array}$	Imidazole at pH 7.4	2.0%	Eye Intradermal	None None	None of 1:1,1000 None of 1:50,000
4.	Mixture of Imidazole and Ethyl amine at pH 7.4		1.0% 0.75%	Eye Intradermal	None None	None of 1:1,000 None of 1:50,000
5.	$\begin{array}{c} \text{HC}=\text{C}-\text{CH}_3 \\   \quad   \\ \text{HN} \quad \text{N} \\ \diagup \quad \diagdown \\ \text{CH} \end{array}$	Methyl Imidazole at pH 7.4	1.0%	Intradermal	None	No inhibition of 1:50,000 histamine
6.	$\begin{array}{c} \text{NH}_2 \\   \\ \text{H}-\text{N}-\text{C}-(\text{CH}_3)_3-\text{C}-\text{COOH} \\   \quad   \\ \text{H} \quad \text{H} \end{array}$	Arginine	0.5% at pH 7.4	Intradermal	None	None of 1:50,000. None of 1:10,000 by electrophoresis also.

7.	$\begin{array}{c} \text{HC}=\text{C}-\text{CH}_2-\text{NH}_2 \\   \\ \text{HN} \quad \text{N} \\ \diagup \quad \diagdown \\ \text{CH} \end{array}$	(Protolistanine) Imidazole methyl amine at pH 7.4 prepared by Prof. H. T. Clarke.	0.1 %	Intradermal	None	No inhibition in mixture by 1:2,000 protolistanine of 1:200,000 histamine. No protection against intravenous histamine.
8.	$\text{HC}=\text{C}-\text{CH}_2-\text{CHO}-\text{COOH}$	Imidazole Lactic Acid pH 7.4	0.5 %	Intradermal	None	No inhibition of 1:50,000
9.	$\begin{array}{c} \text{H} \quad \text{NH}_2 \\   \quad   \\ \text{HC}=\text{C}-\text{C}-\text{COOH} \\   \quad   \\ \text{HN} \quad \text{N} \\ \diagup \quad \diagdown \\ \text{CH} \end{array}$	Histidine Histidine at pH 7.4	2.5 % 0.5 %	Eye Intradermal	None None	None of 1:1,000 None of 1:50,000 None of 1:10,000 by electrophoresis
10.	$\begin{array}{c} \text{NH}_2 \\   \\ \text{CO} \\   \\ \text{NH}-\text{CH}-\text{NH}-\text{CO} \end{array}$	Allantoin	0.5 %	Intradermal	None	No inhibition of 1:50,000 histamine
11.	$\begin{array}{c} \text{NH}-\text{CH}_2 \\   \\ \text{CO} \\   \\ \text{NH}-\text{CO} \end{array}$	Hydantoin	0.5 %	Intradermal	None	No inhibition of 1:50,000 histamine
12.	$\begin{array}{c} \text{H} \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{H} \\   \quad   \quad   \quad   \quad   \quad   \\ \text{O}=\text{C}-\text{C}=\text{C}-\text{C}-\text{C}-\text{CH}_2\text{OH} \\   \quad   \quad   \quad   \quad   \\ \text{H} \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{H} \end{array}$	(Ascorbic acid) Vitamin C	1.0 %	Intradermal	None	No inhibition of 1:50,000 histamine
13.	$\begin{array}{c} \text{N}-\text{CH} \quad \text{CH}_3 \\    \quad   \\ \text{HC}-\text{C} \quad \text{C}=\text{C}-\text{CH}_2\text{CH}_2\text{OH} \\   \quad   \quad   \\ \text{N}=\text{C}-\text{NH}_2 \quad \text{CH}-\text{S} \end{array}$	(Thiamin) Vitamin B <sub>1</sub>	0.6 %	Intradermal	None	No inhibition of 1:50,000 histamine

## PHARMACOLOGY OF A NEW BRONCHOCONSTRICTOR DRUG, HEXAETHYLTETRAPHOSPHATE

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**B**RONCHIAL spasm and other symptoms of parasympathetic excitation may be elicited by acetylcholine, cholinotropic agents such as pilocarpine or arecoline, and by drugs that prevent the destruction of acetylcholine by cholinesterase, the so-called cholinesterase inhibitors or anticholinesterases. A new and highly effective insecticide, hexaethyltetraphosphate, and probably a number of other similar compounds as yet not investigated from the standpoint of their antiesterase activity belong to the latter group.

The pharmacology of this new bronchoconstrictor, hexaethyltetraphosphate (HETP), has been studied in anesthetized dogs and curarized rabbits. Since this substance is a cholinesterase inhibitor it is expected to potentiate the effects of intravenously injected acetylcholine as well as effects following faradic stimulation of parasympathetic nerves. This is, indeed, the case, for hexaethyltetraphosphate in doses of from 0.1 to 0.2 mg. per kg. potentiated the vasodepressor, bronchoconstrictor and other effects of acetylcholine or converted ineffective doses of acetylcholine into effective ones. The same is true of peripheral vagus stimulation, which is markedly potentiated by HETP. This anticholinesterase is capable of exerting intense parasympathetic stimulating effects also without a previous or subsequent acetylcholine administration; a dose of HETP of 1 mg. per kg. being almost immediately fatal in an anesthetized dog due to bronchial spasm and cardiac arrest. However, since doses of HETP of from 0.1 to 0.3 mg. per kg. produce no independent parasympathetic effects when administered alone, the margin of safety for this substance appears to be narrow.

Large doses of acetylcholine in atropinized animals are capable of stimulating autonomic ganglia and skeletal muscle. This effect, otherwise known as the nicotinic effect of acetylcholine, is potentiated by HETP. Doses of acetylcholine ranging from 0.0005 mg. to 0.05 mg. per kg., which in atropinized animals never produced a rise in blood pressure or other signs and symptoms of sympathetic ganglionic stimulation, are pressor in nature following premedication with HETP. To illustrate, a dose of 0.025 mg. per kg. of acetylcholine which produces no effect in atropinized animals produced a rise in blood pressure of over 100 mm. Hg. following 0.25 mg. per kg. of HETP. The optimum dose of HETP for the potentiation of acetylcholine pressor effects is about 0.25 mg. per kg. Doses larger than that do not appear to increase the magnitude of the acetylcholine pressor effect.

The anticholinesterase action of HETP suggested its use as a possible antidote in curare poisoning. A dose of 0.2 mg. per kg. of HETP administered two to six minutes before curarization with a lethal dose (2 units per kg.) of d-tubocurarine chloride saved the life of the poisoned rabbits. However, this dose of HETP was not capable of preventing ataxia, respiratory depression and partial muscular paralysis with collapse, from which the animals recovered in about an hour. With larger doses of HETP (0.3 to 0.4 mg. per kg.) administered prior to curarization the animal did not collapse. In one case HETP administered one minute after curarization also antagonized the effect of the lethal dose of d-tubocurarine.

The comparison of hexaethyltetraphosphate with other anticholinesterases reveals that it resembles more closely the reversible inhibitor of the physostigmine type than the irreversible inhibitor of the diisopropylfluorophosphate (DFP) type. The antiesterase activity of HETP is greater than that of DFP, the minimum effective dose for the elicitation of acetylcholine pressor effects being 0.05 mg. per kg. and 0.5 mg. per kg., respectively.<sup>2,3</sup> The smallest doses exerting maximum effects appear to differ even more widely (0.25 mg. per kg. of HETP as against about 15 mg. per kg. for DFP). The range of effectiveness of HETP is, however, quantitatively comparable to that of physostigmine. It should be noted that a recent publication<sup>1</sup> shows the effectiveness of HETP on the cholinesterase inhibition *in vitro* and *in vivo* and states that (a) it is more powerful than DFP, (b) that the slopes of curves for *in vitro* inhibition of cholinesterase are similar for HETP and DFP, and (c) that DFP has a longer duration of action than HETP. The above experiments confirm the first conclusion of this report.

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## THE USE OF THE RESPIRATORY ENZYME, CYTOCHROME C, IN DYSPNEA

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BASED on the observation that the dyspnea noted in some patients with emphysema seemed greater than would be expected from their vital capacity, it was argued that injections of the respiratory enzyme, Cytochrome C, might enable them to effect more rapid absorption of the



oxygen in inspired air; both for these patients and perhaps also those with bronchial asthma. Five patients were given 10 c.c. of Cytochrome C intravenously at daily intervals for ten days. They were purposely chosen to represent each of the following categories: bronchial asthma due to inhalant sensitivities with no obvious emphysema; bronchial asthma due to inhalant sensitivities with obvious emphysema; bronchial asthma associated with chronic bronchitis, pansinusitis and moderate emphysema with no sensitivities; chronic bronchitis with emphysema associated with wheezing; and coronary heart disease with typical clinical history and electrocardiographic changes.

The patient with chronic bronchitis and emphysema was greatly improved and has had no recurrence of wheezing or dyspnea for eight months. The patients with chronic bronchitis showed less improvement. The patient with coronary disease has also resumed full activity with no anginal pains on exertion. The two patients with inhalant sensitivities, with or without infection and slight or moderate emphysema, showed no lasting improvement beyond the slight temporary, and perhaps "tonic," effect for several weeks.

Work in progress includes studies for a larger group, including other clinical conditions associated with tissue anoxia. Skin test studies on more than 200 patients have shown no incidence of positive skin reaction or any signs of allergenic sensitivity for the extract, although it is prepared from beef heart.

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## 2-METHYLAMINOHEPTANE (OENETHYL) AS AN AID IN THE DIAGNOSIS AND THERAPY OF HEADACHES ASSOCIATED WITH HYPOTENSION

### A Preliminary Report

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SINCE many patients with hypotension are asymptomatic, the possibility of cephalalgia from this cause is often not considered. Disappearance of the headache on elevating the blood pressure is the crucial diagnostic point. Heretofore, available (aromatic) vasopressors when used in amounts sufficient to effect a significant rise are accompanied by unpleasant side reactions such as nausea, precordial distress, tachycardia, tremor, nervousness, perspiration, et cetera. These are usually so objectionable and confusing to the patient that he is unable to give an unequivocal answer as to the relief of headache.

Oenethyl\* 2-methylaminoheptane, is an aliphatic sympathomimetic amine with a marked and persistent vasopressor action accompanied in

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\*Supplied through the courtesy of the Bilhuber-Knoll Corp., Orange, N. J.

less than 10 per cent of cases with any other significant clinical manifestations. Divided doses of 5 to 10 mg. are given slowly intravenously with a continual check on the blood pressure up to a total of 25 to 50 mg., sometimes followed by an intramuscular dose of 50 to 75 mg. to obtain a prolonged effect. The disappearance of the "hypotension" headache is usually noted within three to four minutes, concomitantly with the rise in pressure. The more depressed the original blood pressure, the more notable the effect.

Hypotension is so common among allergic individuals that the term "vagotonic" is often used to describe the group. Since many patients with migraine and headaches secondary to allergic rhinosinusitis may also have more or less constant dull headaches associated with hypotension, it is important for the clinician to evaluate and if possible control this latter factor.

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## PARENTERALLY INDUCED DRUG REACTIONS

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DRUG allergy may be divided into an atopic type and an acquired type. Sensitivity may be induced by inhalation, ingestion, contact with or parenteral injection of a drug. Regardless of mode of sensitization, parenteral injection may induce the allergic reaction. Excepting patch tests, skin tests to drugs are usually negative. Nevertheless, the responsibility of injections is the doctor's; patch or intradermal tests with non-irritating drugs are warranted, especially for common offenders like pituitrin, insulin, penicillin, liver extract, vitamin B complex and the arsenicals. Parenterally induced reactions are those common to drug allergy, i.e., fever, skin eruptions, arthralgia, et cetera, with the added danger of anaphylactic type reactions which may prove fatal.

Three reactions are reported. The first occurred after a pituitrin injection in postpartum bleeding, and consisted of pruritus, tachycardia, tremors, urticaria and angioneurotic edema. Vasomotor rhinitis was diagnosed previously with negative skin tests. Intradermal and passive transfer tests to pituitrin were negative. The second reaction occurred in a woman with arthritis after injections of Vitamin D in sesame oil. It was characterized by a painful indurated erythematous area at site of injections, an Arthus reaction. Family history positive for allergy was negative in the patient except for upset stomach from sesame. Two years later, the patient developed pollen asthma. Skin tests to sesame oil were positive but the oil had whealing properties. The third reaction occurred in a woman sensitized years before to butesyn picrate. Injection of zylecaine containing butesyn, for rectal itch, resulted in vesiculo-papular rash, angioneurotic edema and

## REPORTS IN BRIEF

fever. Skin tests were negative for procaine, peanut, and benzyl alcohol found in Zylecaine. Patch test to butesyn picrate gave marked delayed reaction.

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### METRORRHAGIA DUE TO ALLERGY TO COLD

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**S**YMPTOMS of physical allergy are thought to be mediated through the action of histamine. Histamine stimulates the human uterus resulting in strong contractions. It is not improbable, if unusual, therefore, that an allergy to cold, should result in uterine bleeding.

A young woman, aged sixteen, white, virginal, began menstruating regularly at twelve. In April, 1946, she began swimming in the cold school pool twice weekly. Each swim resulted in uterine bleeding lasting ten hours, never accompanied by symptoms of shock. A vacation from swimming meant freedom from bleeding.

Personal and family history were negative for allergy. Physically, the girl was normal. An intradermal test for histamine sensitivity was negative. A thirty-minute cold bath at home resulted in uterine bleeding. Histamine, 0.4 mg., was injected subcutaneously. Uterine bleeding lasting an hour started one and one-half hours later. Simultaneously with histamine desensitization injections, graduated soaking of the hand in cold water was tried, starting with one minute. After four days she had reached five minutes of inundation, and uterine bleeding started lasting twenty minutes. Shortly, thereafter, she had a normal period, after which she could soak her hands up to twenty minutes without bleeding.

She returned for treatment after swimming for the first time in three months. Her metrorrhagia had returned. She has not been seen since.

There were no blood or endometrial studies performed in this case. The fact that directly after her period the patient could relatively tolerate cold suggests that a secretory phase of the endometrium was necessary to complete the allergic reaction.

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### INSTRUCTIONAL COURSE ABSTRACTS AVAILABLE

A complete set of forty-five comprehensive abstracts of the lectures, with illustrations, delivered at the Cincinnati Fall Instructional Course is now available. The supply is limited. Complete set, \$10.00. Orders should be addressed to American College of Allergists, 423 La Salle Medical Building, Minneapolis 2, Minnesota.

# Editorial

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## THE PRESENT STATUS OF CERTIFICATION

On March 1, 1943, the American College of Allergists, Inc., was incorporated to "establish an organization of qualified physicians and scientists who shall meet for the purpose of promoting and advancing the study, research and clinical knowledge of allergy as it applies to the various specialties in medicine; to maintain and advance the highest possible standards among those engaged in the practice of allergy; to perpetuate the best traditions of medicine and medical ethics; to establish standards for the qualification, and procedures for the certification, of men engaged in the specialty of allergy; to maintain the dignity and efficiency of this specialty in its relation to public welfare; to promote friendly intercourse among those engaged in the practice of allergy."

In less than five years the membership of the College has increased to over seven hundred. Its roster contains many outstanding allergists noted for their accomplishments in both the investigative and clinical fields of allergy and allied subjects. A relatively large number of this group are certified by the various Specialty Boards, a representative group are sub-certified in allergy, and many occupy important positions in teaching institutions and on the staffs of our accredited hospitals.

An intensive educational program has been executed by the College, including an official publication, the *ANNALS OF ALLERGY*, the holding of annual meetings of a highly scientific nature, the conducting of intensive instructional courses in allergy under the auspices of accredited medical schools throughout the United States, the establishment of research fellowships, visiting clinics, and a Speakers Forum.

It was natural, therefore, that the time had come when autonomy in allergy should be recognized. In 1945, the American Society of Certified Allergists was established as a division of the American College of Allergists, Inc. This now has a membership of about 120, who compose the Founders' Group. This group was selected by a board of allergy specialists, certified by their respective boards, sub-certified in allergy, and in addition recognized by their colleagues as physicians meeting the great trust and responsibility for choosing a Founders' Group. With the exception of a few allergists who had practiced allergy for ten years or over and who have furnished evidence of research in allergy, publications on the subject and other essential requirements, all composing this group had been certified by their respective Specialty Boards.

The standards have been considerably raised and require a knowledge of allergy greater than that demanded by the committee on sub-certification in allergy. The College has conscientiously endeavored to meet all of the

requirements necessary for proposal to the Advisory Board for Medical Specialties and to the Council on Medical Education and Hospitals of the American Medical Association.

The American College of Allergists, therefore, has formally proposed to the Advisory Board for Medical Specialties and to the Council on Medical Education and Hospitals of the American Medical Association for their official approval of an American Board of Allergy.

Efforts by the College in this direction have been supplemented and encouraged by a resolution passed by our contemporary society, the American Academy of Allergy, at the business meeting of their fourth annual meeting in St. Louis, December 15, 1947, to the effect that a committee be appointed to make a similar proposal within thirty days for the establishment of an American Board of Allergy to the Advisory Board for Medical Specialties and to the Council on Medical Education and Hospitals. The favoring of an American Board of Allergy by the American Academy of Allergy reverses its hitherto approved policy of sub-certification in allergy. With the high standards maintained by both the College and the Academy, this represents a step toward proper recognition of allergy as a distinct and separate specialty as it applies to the various specialties in medicine.

F. W. WITTICH, M.D.  
Secretary-Treasurer, American  
College of Allergists

## THE PRESENT STATUS OF CERTIFICATION

The American College of Allergists was incorporated in the State of Minnesota on March 1, 1943. One of the motivating purposes of the corporation clearly stated in its charter is that it is legally empowered to establish standards for the qualification and procedure for the certification of men engaged in the specialty of allergy. This was accomplished through the American Society of Certified Allergists and its independent American Board for the Certification of Allergists, both divisions of the College. These divisions were formed in January, 1946, and are still active. The reason for activating these divisions then was based upon the unmistakable need and wish of the majority of the physicians practicing allergy as a specialty.

Our aims and ideals on certification were announced in the January-February, 1946, issue and in the November-December, 1946, issue of the ANNALS OF ALLERGY. To quote one pertinent and timely statement, "We hope that the Advisory Council of the American Specialty Boards will accept in our favor the logic of the situation as it is. All we did for allergists is what the majority of allergists wanted—autonomy in the matter of certification. . . . Reconciliation of a Board for the certification of allergists as an autonomous Board within the framework of the Advisory Board on Medical Specialties is a just solution and the problem should not be too difficult to resolve. It is a task worth accomplishing since the

alternatives are in disharmony with the needs of American Allergy." We continued to remain steadfast to the proposition that if allergy is to survive as a specialty, it can do so only as an autonomous specialty.

With the passing of each month, increasing numbers of allergists throughout the country have joined the crusade to practice allergy as a dignified specialty. With such support, the American College of Allergists grew and the American Society of Certified Allergists has well over 100 members who are representative of American allergy in its finest phases.

Now that the majority of the allergists in America are enlisted in support of an autonomous Board of Allergy and since it is clearly stated in the above mentioned issues of the ANNALS OF ALLERGY that the creation of our independent American Board for the Certification of Allergists was a means to an end, and in no way could be construed as a movement in defiance of "organized medicine," we, in the American College of Allergists have every reason to remain loyal to the allergists of America and will continue to labor unstintingly for autonomy in certification of allergists.

The editorial in the *Journal of the American Medical Association* outlined the steps for an application for an Allergy Board. In December, 1947, the American College of Allergists and its affiliate, the American Society of Certified Allergists, formally applied to the Advisory Board for Medical Specialties of the Council on Medical Education and Hospitals of the American Medical Association for the formation of an autonomous American Board of Allergy.

We have been patient a long time. The moment has come to implement in favor of an autonomous Board of Allergy within the framework of the American Medical Association.

Meantime, we note that our contemporary, the American Academy of Allergy, during the business session of the meeting held in St. Louis, Missouri, December 15 to 17, 1947, adopted a resolution to make formal application to the Advisory Board for Medical Specialties for an autonomous American Board of Allergy. This action, along with the previous similar action of the American College of Allergists, unites an unmistakable majority of American allergists in support of an autonomous Board of Allergy.

The American Society of Certified Allergists, an autonomous society, and the only society of certified allergists, invites all allergists who are not now members and who have been certified in allergy to become members. Your interests as certified allergists can be best served and protected by uniting with your fellow colleagues who are certified.

Remember that the specialty of allergy can only endure as a dignified specialty if it is an autonomous specialty practiced by allergists who are united in purpose and meet each other in harmony and respect. We have made a start. Let us keep it that way for all time.

M. MURRAY PESHKIN, M.D.  
Secretary-Treasurer, American  
Society of Certified Allergists

# Progress in Allergy

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## DERMATOLOGIC ALLERGY

RUDOLF L. BAER, M.D., F.A.C.A., and MORRIS LEIDER, M.D., F.A.C.A.

New York, New York

This review of progress on dermatologic allergy for the past year (about July, 1946, to date) is not complete in the sense that every published item on the subject has been examined, listed and commented upon. However, an attempt was made to examine most articles in the available literature and those that seemed most significant were selected for more extended treatment. The subject matter has been divided into arbitrary topics merely as a convenient device for discussion, and to indicate those topics which at the moment seem to present the best opportunities for further study and progress.

### THE GENERAL THEORY OF ALLERGY AND OF THE ALLERGIC MECHANISM

In these first postwar years, when research and study are being resumed at accustomed peacetime pace and without the peculiar selection necessitated by the war period, it appears important to the progress of allergy that one reconsider the present definitions of the term "allergy." The tendency of recent years has been to mistakenly equate allergy with hypersensitivity and with certain disease processes only and at that with diseases of sometimes complicated diagnostic routines or uncertain therapeutic possibilities. The allergic state as a desirable and clinically beneficial transformation is hardly considered or presented at all. At the same time this narrowing of the concept of allergy in some quarters is matched with a naïve avidity on the part of the general lay public for ready explanation of all disease by "allergy," on a part with such trite explanations like "acid in the system," "nerves," et cetera. Thus the word allergy in the popular mind has come to be almost synonymous with "dislike." People say they are allergic to strawberries and to mothers-in-law, to mention but two popular allergens. It has even been said that some physicians have become allergic in this sense to allergy.

Several recent articles and textbooks deal with basic concepts and formulations of the theory of allergy. It is unfortunate that some experimentalists and theoretical immunologists have narrowed the concept of allergy in a way which tends to mislead the practicing allergist in the matter of the interpretation of the phenomena of allergy. Needless to say, it is not necessary to dispute the facts gleaned from the laboratory in order to disagree with the way these facts are integrated into working theories. Often it is not a question only of who is right or wrong; rather, who has the most logical and fruitful approach.

Some workers tend to make allergy equivalent to conditions of hypersensitivity, i.e., conditions of clinical allergic disease, and do not include conditions of clinical cure or prevention and prophylaxis of disease that are of exactly similar mechanism. It is unfortunate that some practicing allergists who are concerned with effecting cure and prophylaxis of allergic disease should follow these limited formulations and thus fail to see that hyposensitivity and immunity as allergically derived conditions, naturally occurring or therapeutically induced, are equally or perhaps even more important to explore and include in allergy.

To be specific, what is allergy? Let us set down some representative definitions. Topley and Wilson,<sup>85</sup> representing the thought of immunologists, write: "The term *allergy* is almost impossible to define. Here we are using it in a

loose, but widely accepted sense to cover a group of reactions characterized by a heightened or accelerated (clinical?—Ed.) response to a particular type (what particular type?—Ed.) of antigen, irrespective of the balance of harm or benefit that the altered response confers on the allergic host." Other texts on immunology, e.g., by Gay, Zinsser and Kolmer, define allergy as hypersensitivity with even less qualification. Landsteiner,<sup>48</sup> as an example of the experimentalists's view, relegates the definition of allergy to a footnote which reads as follows: "Hypersensitivity in man is often distinguished by the name of 'allergy' but this term—originally meaning increased as well as diminished reactivity (Pirquet)—is also applied to hypersensitivity in general, usually with the exclusion of typical, anaphylaxis." Feinberg,<sup>27</sup> a clinician, states: "Allergy, in its broad implication, designates hypersensitiveness in man and evidences itself by abnormal responses of tissues to physical or chemical stimuli." Tuft's<sup>86</sup> and Cooke's<sup>16</sup> books express nearly the same idea. Rich<sup>68</sup> represents a school of thought which would like to dispense entirely with the word allergy for the reason that it has become "debauched," to use Rich's expression. Within the vagueness of these definitions, we gather that allergy is, by and large, taken to mean clinical hypersensitive states.

Others conceive of the allergic state as any pathologic clinical condition wherein antigen-antibody interaction can be demonstrated and proved causative. Where antigen-antibody interaction is not yet proved in cases of indisputable hypersensitivity, it is conceded, or presumed, that ultimately an antigen-antibody reaction will be demonstrated. Thus Doerr<sup>22</sup> concludes: "It seems to me permissible, when the demonstration of an antibody is not possible, or not constantly possible, to take refuge in the consideration that the (allergic) phenomena observed in both man and animals cannot be explained in any other way than by the supposition of a *pathogenic*† antigen-antibody reaction." Here we see that two of the cardinal tenets of allergy according to this concept are pathogenicity and antigen-antibody reaction. Boyd<sup>12</sup> follows this formulation. He defines immunity as resistance whereas allergy is hypersensitivity. All this is done despite the fact that the data presented by some of these authors themselves show that the mechanisms of immunity and hypersensitivity (their allergy) are parallel and comparable.

It seems obvious that there must be a generic word to describe both phenomena of immunity and hypersensitivity when either develops and persists by similar mechanism no matter what "the balance of harm or benefit the altered response confers on the allergic host." That word is allergy. To reduce its meaning to the level of hypersensitivity is restrictive. It removes the special connotations of "altered" and of "specifically acquired" which are inherent in the word allergy and add to hypersensitivity the quality of "specificity" which is not inherent in that word. Making allergy generic for both specifically acquired immunity and hypersensitivity permits a better understanding of certain immunizing procedures as beneficial allergic changes. Moreover, it does not prejudice clinical hypersensitivity as being necessarily harmful.

The reviewers adhere to the original concept of allergy as formed by von Pirquet<sup>89</sup> and Schick, and as interpreted by Sulzberger,<sup>79</sup> which in its simplest and most inclusive form defines allergy as any specifically acquired alteration in the capacity of living tissue to react to a substance, which substance may be animate or inanimate. In another connection<sup>52</sup> the following clarifying qualifications have been added to this definition: The words "alteration" and "specifically" connote (1) that the new capacity to react is ordinarily relatively constant and lasting and is always characteristically different, clinically or by laboratory evidence, from the original capacity to react; (2) that the new capacity to react may be clinically greater

†Our italics.—EDITOR.



or less than originally; (3) that the new capacity to react is in some essential way dependent upon an original or previous exposure to the same or an immunologically related substance; and (4) that the new capacity to react becomes manifest upon re-exposure only to the same or an immunologically related agent. Two other helpful criteria<sup>70</sup> may be added as follows: (1) the development of allergic states is characterized by a fairly constant incubation period which is, in most instances, between five days and three weeks no matter what the form of the new capacity to react; and (2) the elicitation of the several types of allergic states is attended by a characteristic reaction time, depending in character upon the type of allergic state induced or present.

We believe that this primary definition with its addenda is more flexible for inclusion under one head of a large volume of seemingly unrelated, but immunologically very definitely related clinical and laboratory phenomena. It provides a unitary theory explaining certain responses of the organism to foreign substances on the basis of the nature of the response rather than on the nature of the substances themselves or teleology with reference to the organism involved. A better terminology and language of communication can be built up from a concept wherein both hypersensitivity (often leading to clinical disease but sometimes beneficial) and hyposensitivity or immunity (often leading to nonoccurrence of disease or at least an attenuated form of disease but sometimes harmful) are included under the one head of allergy and considered as opposite poles of specifically altered reactivity.

The terms sensitivity, hypersensitivity (hyperergy), hyposensitivity (hypoergy), anergy (insensitivity), et cetera, are in themselves descriptions which imply a point of reference that is comparative. The proper way to employ the words hypersensitivity, hyposensitivity and normergy is by qualification of each when used by the adjectives allergic or nonallergic. The rest of the language of immunology may thus properly be converted for use in allergic connotations when indicated, or left for use in nonallergic senses when that is proper. To insist on pathogenicity as a hallmark of allergy amounts to removing immunity from the field of study of allergy and destroys continuity in research and understanding. That this was not intended by those who were imaginative enough to originate the concept of allergy<sup>80</sup> is shown by the fact that the hypersensitivity as well as the immunity after smallpox were cited as characteristic examples of allergy. To insist further upon demonstration of an antibody as proof of an allergic state at this stage of development of the subject is to cast out a large number of disease entities, particularly *dermatoses*, which clearly fulfill every other criterion of allergy, even in the limited sense of the experimentalists. However, it must be admitted that the concept of the presence of as yet undetermined antibodies in these disease entities is logical and fruitful.

Once the problem of how the theory of allergy is most correctly formulated is agreed upon, then discussions like that of Hooker<sup>43</sup> become understandable and meaningful. Hooker's paper reviews the contributions of Landsteiner, with proper panegyrics to their brilliance, and shows how the chemo-physical properties of haptens, antigens and antibodies, the characteristics of colloid behavior, the spatial arrangements of globulin molecules and the lattice theory of antigen-antibody interaction explain much of allergic behavior. Revealing work along these lines following clinical leads and furnishing in return clinical clues, in a ceaseless to and fro catalysis of observation and experimentation, is what may be expected as the pure sciences are applied more and more to the field of dermatologic allergy.

In a similar way, Miller and Campbell<sup>59</sup> interpret experiments to support a theory that reagin antibodies are peculiar and different from "normal" antibodies in that they are the result of a distorted or incomplete antibody-forming mechanism, i.e., reagins are characterized by unipolar combining groups and therefore have dif-

ferent clinical and laboratory characteristics, e.g., (1) they are heat labile; (2) their formation depends on an inherited disposition; (3) they do not produce precipitate with specific antigen; (4) they are skin sensitizing, and (5) they do not neutralize specific antigen. As the situation stands there is much left to be desired in such an explanation. For instance, what is meant by a "normal" antibody? Is such an antibody inevitably neutralizing, i.e., one which binds antigen so that clinical disease is prevented or cure effected? Such are the antitoxins, blocking antibodies and other neutralizing antibodies generally. The premise that reagins are "abnormal" and are only found in those with an inherited disposition is not correct as reagins are found in a great number of nonatopic human beings when they are exposed to certain agents (*ascaris*, et cetera).

Scherago<sup>73</sup> discusses the problem with respect to bacterial allergy and comes to the following conclusions: "Of the five types of bacterial hypersensitiveness, three (anaphylaxis, atopy and heterophile toxicity) do not differ materially from their prototypes to nonbacterial agents. The other two (tuberculin-type and Schwartzman-type) have thus far been induced and elicited only with micro-organisms and their products. It is possible that underlying all types of hypersensitiveness is a common basic principle, namely, that the exposure of the tissues to an undigested foreign or abnormal substance stimulates the production of specific antibody, different for each substance, and that the different forms of hypersensitivity reactions are effects that result from the interaction of antibody and antigen under different conditions." Again, there is much that may be argued pro and con here. Although Scherago considered only hypersensitive states, we miss at least passing mention of antigen-antibody interactions that end in clinical insensitivity. We miss it if only as a realization that these too are common "effects that result from interaction of antibody and antigen under different conditions." Also tuberculin type sensitivities often have been duplicated with nonbacterial substances (Frei, Sulzberger, R. L. Mayer, Landsteiner and Chase, Epstein<sup>26</sup>). The Schwartzman phenomenon on the basis of the definition of allergy previously discussed is a non-allergic event as the alteration in the capacity to react is not *specifically* acquired. We wonder, too, what is meant by "different conditions." Are different shock organs implied? And we doubt that "undigested foreign proteins" or "abnormal substances" can be presumed to evoke just one type of antibody differing only in specificity and in that the reaction type is determined by "different conditions."

An interesting observation is reported by Birkhaug and Bøe<sup>10</sup> demonstrating that the induction of an allergic state to BCG and anaphylactic sensitization in guinea pigs with horse serum both produce a restricting influence in the skin to the spread of nonspecific vital dyes. Moreover, specific desensitization of the bacterial allergic state and of the anaphylaxis abolishes the restricting capacity of the skin to the spread of nonspecific vital dyes. The interpretation of this phenomenon is left open but interesting speculation can be made about the nonspecific alterations in physiology that results from allergic states. For example, in recent years the enzyme hyaluronidase has received attention as probably being the "spreading factor."<sup>25</sup> For nearly twenty years it has been known that injection of suspensions of bacteria or India ink together with the "spreading factor of Duran-Reynals" promoted invasion of tissues. Can it be that certain allergic hypersensitive states as anaphylaxis and tuberculin sensitivity inhibit the spreading factor and in this manner produce nonspecific protective, immune effects rather than purely baleful effects?

#### THE HISTAMINE THEORY OF ALLERGY AND THE SO-CALLED ANTIHISTAMINICS

The original demonstration of the similarity of action between histamine and anaphylactic states has led to an astounding readiness to reason that this substance, or hypothetical H substance, is the basis of allergic hypersensitive states. And

by making the error of equating hypersensitivity with allergy, the tendency has been to regard histamine or H substance as the mediator in allergic reactions in general. Without consistent chemical evidence, histamine or H substance is presumed to be released in reaction-producing amounts as a result of the antigen-antibody interaction or, if released in physiologic amounts, to be accompanied by hypersensitivity to it (allergic or nonallergic?).

While there is some evidence which supports the histamine theory in dermatologic allergic states that are characterized by whealing, the facility with which it has been applied in nonurticarial dermatologic allergic states is to our minds not warranted. Although the presence of histamine in the normal skin has been proved, there is up to this time no evidence that in the nonurticarial forms of dermatologic allergic reactions (eczematous, tuberculin-type, et cetera) histamine is released in abnormal quantities or that the tissues are abnormally sensitive to histamine or, most important, that histamine has the inherent capacity to produce the reactions which are seen clinically. The advent of the so-called antihistaminic agents has led to renewed experimental and theoretical consideration of the role which histamine might possibly play in nonurticarial allergic dermatoses.

R. L. Mayer<sup>56,57</sup> concludes: "antihistaminic substances which are a very important addition to the therapy of allergic diseases also constitute a very useful tool for the study of allergic conditions. Its use enables us to detect the activity of histamine or H-like substance and its role in various allergic diseases. During the investigation it has been shown with the help of this tool, that histamine or H-like substance is not only an important factor in anaphylaxis and allergic manifestations which are closely related to anaphylaxis but also in certain other manifestations which until now have not been associated with histamine. Indeed Pyribenzamine, a substance exhibiting strong and specific antihistaminic properties, exerts a definite activity in experimental dermatitis. This fact suggests that H substance also plays an important role in contact dermatitis thus connecting this disease to anaphylaxis and other allergies of an anaphylactic nature."

Great caution is essential in drawing any conclusions from Mayer's interesting work. There is no challenging Mayer's results proving that Pyribenzamine is effective in partially preventing contact dermatitis under the conditions of his experiment. However, it must be remembered that experimental contact dermatitis in guinea pigs' skin may have an urticarial component similar to the urticarial component in many cases of allergic eczematous dermatitis in man. But the deduction from these observations that histamine or H substance consequently is implicated in the production of allergic eczematous dermatitis is in our opinion not warranted. A paper by Brown<sup>13</sup> reasons the same way in what is termed "emotionally" precipitated urticarial conditions. For, a similar case can be made out to show that other hypothetical substances, not histamine, are basically involved in anaphylaxis for instance because Adrenalin, ephedrine and anesthetics also inhibit or interrupt anaphylaxis. It is universally conceded now that the so-called antihistaminics abate many cases of urticaria. The possibility that this is so because of other properties rather than by interference with the action of histamine has been mentioned by Sulzberger.<sup>83</sup> Leavitt and Code<sup>49</sup> have shown a marked local anesthetic action from Benadryl, and Code recently stated that the antihistaminic action of Benadryl and other antihistaminic drugs appears to be independent from their local anesthetic action.

There have been a huge number of papers, of which we cite a few<sup>23,54,64,67,84</sup> on statistical appraisals of clinical results of exhibition of the "antihistaminics" in various diseases, not all allergic. The sum total of the work published on this subject shows that they are desirable and effective palliative agents in about 75 per cent of cases of acute urticaria, about 50 or more per cent of cases of chronic urticaria, and that they are useful antipruritic agents in a small but significant percentage

of other allergic and nonallergic pruritic dermatoses. From the dermatologic viewpoint the greatest disappointment has been their very limited efficacy in the atopic dermatoses.

## ATOPIC DERMATITIS

The role and importance of allergic factors in this disease are often obscure. In many cases we have been unable to discover any evidence implicating allergic factors. The elucidation of the precise mechanism producing atopic dermatitis appears not at hand nor is the hope for new means of therapy any brighter.

Attraction to the psychosomatic explanation<sup>17</sup> for dermatoses of obscure etiology has started all over again since the grim realities of the war years are over. In this field there is a tendency to selfdeluding mysticism and escapist obscurantism. What is the general psychosomatic content of a four-month-old infant with atopic dermatitis, what is that of a six-year-old, an adolescent or young adult with this condition, that distinguishes them from ordinary mortals? How does psychosomatic theory explain the spontaneous abatement of the disease in the large majority of cases in early middle life? Does maturity and insight come naturally at twenty et sequitur? In a large clinic material, ordinary observation of personality revealed no significant differences to the reviewers between persons afflicted with cutaneous atopy and those suffering from any other dermatosis. If anything, the former bear their disabilities with more creditable fortitude than the rest of us.

Hill has written two papers<sup>39,40</sup> which discuss the contradictions between skin test results and the clinical and therapeutic effects of exposure or avoidance of skin test-positive and skin test-negative agents. The dissociation between positive test results and the inefficacy of procedures of avoidance of allergens that are incriminated by test is as distressing to physician as patient.

We have gained the impression that from the viewpoint of the allergist the reasons for the intractable nature of atopic dermatitis are as follows:

1. The number of sensitizations (the number of offending allergens) in some cases may be large and much larger than is indicated by testing, no matter how extensive the testing.
2. The duration of each sensitization may be exceedingly variable, or the level of each sensitivity may be constantly rising and falling. Also, the pattern of sensitization, i.e., the kinds of allergens operative at any one time, fluctuates. For example, one of us (RLB) noted that before the war almost all patients with atopic dermatitis who gave positive scratch test reactions reacted to silk protein, and that during the war and since the war the incidence of such reactions among atopic dermatitis cases fell to zero or close to zero. We attribute this disappearance of silk reactions to the lack of exposure to silk. If this interpretation is correct, then the incidence of silk reactions among our atopic dermatitis patients should increase again with the increasing possibilities of exposure to silk materials.
3. Complete avoidance of all allergens offensive at any given moment is nigh impossible.

As indicated above, the currently available "anti-histaminics" have not significantly changed the therapeutic approach to atopic dermatitis. The direction of environmental control is all the more to be sought if the implications of Simon's work<sup>74</sup> should be confirmed. His studies suggest that persons with atopic tendency may get sensitized to body-own substances (danders) from their fellow human beings, particularly persons *en famille*, and even to themselves! However, Simon has been commendably conservative in his conclusions as to the practical importance of his findings.

There has been a revival of interest<sup>24</sup> in the work of Hansen et al<sup>35,36,37</sup> which suggests that there is a disturbance of fatty acid metabolism in atopic derma-

titis in children. Episodes of clinical activity of the disease have been found to be associated with a low plasma level of unsaturated fatty acids. One possible conclusion is that this circumstance plays a role in producing the disease, and the obvious therapeutic conclusion is to rectify the situation by feeding larger amounts of unsaturated fatty acids. Favorable responses have been reported by the Hansen group. Others<sup>24</sup> have not found the treatment beneficial. The difficulty of administering such an apparently easy treatment is considerable. In a small trial we have noted, as has been noted before, that the feeding of as little as 1 teaspoonful of lard, for instance, induces nausea in a large percentage of cases. If the feeding of saturated fatty acids could be proved to be helpful in good measure, it would pay to experiment with culinary arts and the gastronomies of fat digestion.

Stoesser<sup>75,76</sup> contributed two papers recently on blood lipids and eczema. In the earlier ones he recorded evidence that the course of infantile atopic dermatitis during acute upper respiratory infections shows a relationship with the plasma level of unsaturated fatty acids as determined by iodine number readings on plasma. At the onset of such an intercurrent infection there is improvement in the eczema and this coincides with a flooding of the system by unsaturated fatty acids (high iodine number). Shortly thereafter when the grippal episode ends the eczema worsens as the plasma content of unsaturated fatty acids falls precipitously (low iodine number). In his second communication, Stoesser produced dermatitis in rats on fat-free diets which resulted in low plasma iodine numbers. Cures and higher plasma values followed the addition of unsaturated fatty acids to the diet. When children with atopic dermatitis were fed a soybean preparation of high iodine absorption value, clinical improvement followed together with a rise in plasma iodine number.

Again the question is whether the induced low level of unsaturated fatty acids in the blood is causal of cutaneous exacerbation in atopic dermatitis or whether both events are owing to a common other cause. It would be interesting to see whether severe febrile diseases which are accompanied by improvement in atopic dermatitis (the opposite of the effect of the common cold) are attended by high plasma values for unsaturated fatty acids.

Norrlind<sup>61</sup> published an exhaustive monograph on the effect of acute upper respiratory infections on the course of atopic dermatitis. His studies seem to indicate that sensitization to bacterial antigens is one of the reasons for exacerbations of atopic dermatitis.

#### ALLERGIC ECZEMATOUS CONTACT-TYPE DERMATITIS

This title is taken from the usage developed by Sulzberger.<sup>78,81</sup> "Allergic" connotes specifically acquired alteration in the capacity to react in the senses detailed above. In this type of allergic state a delayed, or late, forty-eight-hour response is characteristic. "Eczematous" means a clinical combination of some of the following: edema, papules, vesicles, oozing, thickening, lichenification, scaling or pigmentation. "Contact-type" indicates that the allergen usually reaches the shock tissue (epidermis?) from without (exogenously). This designation does not preclude the possibility (which is frequently enough the case) of allergen approaching from within (endogenously). The telling point is that in either event the clinical gross morphology is eczematous and that the histopathologic picture is that of epidermal spongiosis in the classical manner. These three modifying adjectives serve to classify more exactly one disease entity which is a part of the large group of eczemas and to distinguish this dermatosis from presumably non-allergic eczemas like the mummular, seborrheic, solar, actinic and caloric. It also serves to separate it from other allergic eczemas of vaguer mechanism like the infectious eczemas and eczematoid processes, like atopic dermatitis.

Compared to atopic dermatitis, allergic eczematous contact-type dermatitis is a much more satisfying and, at the moment, more rewarding field of study. Often the allergens are simple chemical compounds or plants which are readily identified in a high percentage of cases with reasonable detective ingenuity and effort. Patch testing is an easy and, if properly executed, relatively safe confirmatory routine. Cure by avoidance of the offending agent is frequent and dramatic.

However, the problem basic to all hypersensitive allergic states leading to clinical disease, namely, how to reverse the allergic state, i.e., reconstitute the affected individual to the original insensitive or normergic state, remains. Improvement by hyposensitization procedures, as a lesser goal, is also unsolved in allergic eczematous contact-type dermatitis. Antibodies and antigen-antibody interactions are not convincingly demonstrable as yet on this type of allergic state. Controversy has raged on this point for many years. Some<sup>31</sup> claim to have detected antibodies by means of the classical Prausnitz-Küstner experiment with the sera of persons with allergic eczematous contact-type dermatitis; others<sup>38</sup> and recently again Mom and Ballesteros<sup>5</sup> have claimed actual reproduction of the clinical disease, by the Urbach-Königstein modification of passive transfer. We<sup>52</sup> have recently performed similar experiments utilizing the Urbach-Königstein technique with completely negative results, and as is well known W. Jadassohn<sup>46</sup> and Sulzberger<sup>79</sup> have never been able to confirm positive findings claimed despite extensive trials. However, further investigations with new techniques and approaches such as those used by Haxthausen<sup>38</sup> may in the future lend further support to the findings of those who claim to have demonstrated passive transfer antibodies in eczematous dermatitis.

Epstein<sup>26</sup> discusses in a general and speculative way, the other forms of skin test reactions that eczematogenic allergens may produce. In particular he notes delayed, tuberculin-type reactions to intradermal introduction of allergens that ordinarily give eczematous responses to patch tests in persons with eczematous sensitizations. He relates this phenomenon to certain drug eruptions which can then be conceived as tuberculin-type responses to eczematogenic allergens with the difference from allergic contact-type eczematous dermatitis being in that the site of shock tissues is somewhat lower than ordinarily in eczematous dermatitis and that clinically the approach of allergen is from within (experimental deposition is deeper.) It appears possible that the edematous and ~~thematous~~ appearance of some cases of contact-type dermatitis can be explained on the same basis: the site of shock tissue and reaction being, in part, in the capillaries of the papillae of the upper cutis. This position is fairly readily approached from without as well as from within and can explain the urticarial component of some cases of allergic eczematous contact-type dermatitis (e.g., poison ivy dermatitis). These phenomena can be related, as do Epstein and Rostenberg,<sup>70</sup> to the concept of haptens and it may be that the way or variety of ways in which a given eczematogenic allergen combines with larger molecules at any time determines the form and site, or multiplicity of forms and sites, of allergic sensitization and reaction. It is well substantiated from Landsteiner's work and subsequent clinical check that any of several radicles of a chemical complex may act as determinants of specificity of type or form of allergic transformation.

We find a very minor item to quarrel with in Epstein's article. The use of words like "dermitis" and "epidermitis" are philologically peculiar if not absolutely incorrect. The suffix "-itis" does not inherently mean inflammation and though it may be argued that it has acquired that meaning by force of long usage in that sense, it is still unnecessary to compound it arbitrarily to compete with already adequate and philologically proper words like dermatitis. It would be well to realize that "-itis" is a Greek adjectival ending with the force of "relating to," "deriving from," et cetera. The Greeks spoke of *nosos dermatitis* (disease of the

skin, skin disease), *nosos gastritis*, *nosos arthritis*, et cetera. But as is linguistic habit, the adjective has become a noun with the whole meaning of the phrase and signifying inflammation by secondary attribution. The proper stem with which to form words from *derma* is *dermat-*. "*Dermatitis*" and "*epidermitis*" are philologic monstrosities. An article on related problems of technical philology by one of us (M.L.<sup>53</sup>) is in press. Also it is a moot question whether inflammation can properly be spoken of, as occurring in a nonvascular tissue such as the epidermis.

Howell contributed two interesting papers on allergic eczematous contact-type dermatitis. One<sup>44</sup> analysed a fairly large material from private practice which illustrates the great variety of allergenic substances implicated and the high rate of discovery with diligent search. In the other<sup>45</sup> treatment of acute poison ivy dermatitis by injection of "specific" extracts is argued to be theoretically irrational and, more important, shown by clinical trial to be utterly ineffective. Howell also brings simple but the more effective proof that the available commercial extracts vary tremendously in their allergenic potency from one brand to the next and at times from batch to batch of the same brand.

There have appeared several case reports of allergic eczematous contact-type dermatitis which are significant for collateral reasons. Keil, Wasserman and Dawson<sup>17</sup> reported on mango dermatitis and demonstrated cross-sensitizations between the allergenic principles of the mango tree, poison ivy, *bilawanol* oil, cashew nut, et cetera. The botanical connection as *anacardiaceae* is traced and the practical sociologic significance of cross-sensitization is stressed.

The phenomenon of cross-sensitization is receiving more attention at the moment. Very startling and useful facts are being uncovered. For example, Dobkevitch and Baer<sup>21</sup> described contact dermatitis due to the azodyes in nylon stockings and have discovered cross-reactions between paraphenylenediamine and the azodyes commonly used in nylon stockings. The chemical and biologic reasons for such cross-reactions were presented in 1928 by R. L. Mayer. More work is in progress in the same direction by Baer and coworkers on similar cross-reactivity between the above dyes and the azodyes used to color everyday foods, drugs and cosmetics. It is possible that some cases of dermatoses that have been attributed to food sensitivity may turn out to be due to ingested food dyes that evoke allergic eczematous contact-type dermatitis in persons with eczematous sensitization by endogenous approach of the simple chemical allergens.

This leads directly into eczematous dermatitis due to "food allergy" which has had many proponents. Everyone has seen cases which patients claimed were due to the ingestion of particular foods, and many observers have at times accepted such a possibility in certain cases. When a patient claims with great certainty that such and such a food is causative, it has always struck us as peculiar that the eruption is present at all, since, from the very certainty and conviction on the part of the patient of what ails him, one would think the patient would strictly avoid the supposedly offending food and not have the dermatosis. Such, however, is not the case. When a case of urticaria is clearly caused by a food, frequently the patient will know exactly which food, or group of foods, is operative, and clinical testing (not skin testing!) merely confirms, and possibly uncovers, closely related sensitivities. Such patients keep themselves comfortable by avoidance of the obvious and often seek advice only when avoidance is difficult because traces of the food at fault occur in occult manners in other foods or when they seek desensitization because they feel incomplete or imperfect when they cannot ingest, say, kumquats.

The reports by Flood and Perry<sup>28,29</sup> and by Rowe<sup>71</sup> are strongly suggestive of the causal nature of foods in a significant percentage of cases of eczematous dermatitis of the hands. However, much more confirmatory evidence is needed

before the importance of foods in the causation of a significant percentage of eruptions of this type can be definitely accepted. In Rowe's series the long periods of treatment may have been attended by numerous nonspecific beneficial factors. Flood and Perry state that "pyogenic and trichophytic infections are often superimposed on the underlying food sensitivity dermatitis. This must be recognized and eliminated before food testing can be interpreted." One may ask how such superimposed pyogenic and fungous infections can be recognized and eliminated with certainty.

The question of eczematous eruptions of the hands caused by foods is a complex one. Among the factors in foods which may conceivably be the causes of such eruptions are not only the "protein" fraction and the "oil" fraction or some other fraction in the raw materials of the food but also adjuvants such as preservatives (benzoates, saltpeter, et cetera), antimolds (propionic acid, et cetera), dyes (azodyes, et cetera; see above) and agents used in the preparation of the foods (bromates, iodized salt, et cetera). Not only must these and other factors be considered as *ingested* articles but if the food is at all handled by the patient they may also become causal factors by simple *contact* with the hands.

The matter must remain *sub judice*. More clinical observation, histologic studies and patch, scratch and intradermal testing with all the factors listed, are necessary to bring further supportive proof that ingested food (protein) allergens are capable of producing allergic eczematous dermatitis, in addition to the well-recognized usual urticarial and atopic dermatoses.

The same difficulties mentioned in connection with eczematous eruptions of the hands due to foods apply to the findings and conclusions of Rugeley<sup>72</sup> on food allergy as a cause of pruritus ani. That some cases of pruritus ani may be due to food sensitivity had been previously suggested. The only proven case of pruritus ani due to a food which one of us (RLB) has seen was a characteristic allergic eczematous contact-type dermatitis in the perianal area due to mango fruit. In this case there was also dermatitis of the perioral area. Much further investigation of cases of pruritus ani for possible food allergy is necessary before definite conclusions can be drawn from Rugeley's findings.

Sulzberger, Kanof, Baer and Lovenberg<sup>82</sup> report on sensitization to sulfonamides from topical application. They conclude: (1) As regards the incidence of sensitization on topical application, the sulfonamides tested can be arranged in order of increasing sensitizing potential and this order corresponds to increasing solubility in water. The order is sulfadiazine, sulfathiazole, sulfanilamide, sodium sulfadiazine. (2) Cross-sensitization to other related compounds occurs with significant frequency after exposure to a sulfonamide. (3) Preceding more or less superficial skin damage at the site of topical application is a powerful influence in increasing the incidence of sensitization by externally applied sulfonamides. (4) Previous exposure to and/or skin sensitization by externally applied sulfonamides materially increases the risk of cutaneous and general reactions on subsequent oral administration of the same or related drugs.

Another paper by Philips<sup>66</sup> on the same subject contains valuable clinical and test observations.

Hinman<sup>42</sup> counted a 4.5 per cent incidence of eczematous dermatitis in personnel who refinished the stocks of captured Japanese rifles. The high incidence in those known sensitive to poison ivy and poison oak is noteworthy. It is interesting to speculate what was the incidence of contact-dermatitis from this circumstance among Japanese soldiery and what amount of military help our forces received from this windfall of enemy disability.

Rostenberg<sup>69</sup> recounts the occurrence of eczematous sensitization to natural hair of several animals, namely, the coati-mundi, raccoon and skunk. The zoologic relationship is traced. The allergen was found not to be soluble in acetone or ether.



Leider<sup>51</sup> reported what is believed to be the first proved case of epidermal sensitization to DDT. Criteria of proof are fulfilled including a positive patch test with a standardized test material. The fortunately low sensitizing potential of DDT is remarked.

## ALLERGY TO ANTIBIOTICS

The number of agents that may induce and elicit an allergic state of eczematous hypersensitivity is legion. Sensitization to simple chemical compounds like the inorganic salts of the heavy metals, e.g., mercury, arsenic and nickel (indeed to the elements themselves!) and to still relatively simple organic agents like paraphenylenediamine, quinine, sulfonamides, et cetera, are old stories. Since the advent of penicillin, eczematous sensitizations to comparatively complex compounds like the crystalline salts of penicillin (but still not of the order of protein) and to what must be similar products of other fungi have attracted attention. Particular interest centers about penicillin because of the variety of cutaneous and general allergic states and allergic reactions it may induce and elicit. The importance of this agent in the management of hitherto hopeless disease or diseases that have up to now always resulted in serious permanent morbidity or disability, has led several perspicacious observers<sup>7,15,18,30,32,41,55,58,60,62,63</sup> to discuss and emphasize its high sensitizing potential. This has become all the more pressing because penicillin seems so harmless on first exhibition and is consequently being used recklessly. It would seem that many types of cutaneous and constitutional allergic states have already been observed to be caused by penicillin. It is obvious then that blithe disregard of future consequences in the use of antibiotics is fraught with danger. For, it may soon come to pass that since the over-all sensitizing potential of penicillin seems to be about 5 per cent and since nearly everybody is receiving the agent for trivial conditions and for diseases where it is utterly ineffective, every 20th person may in the future be denied the use of the agent in serious illness because of previous sensitization. It is to be considered too whether the units of morbidity induced by senseless sensitization may not ultimately begin to outweigh the units of benefit. Such lessons should not only hereafter be kept in mind for penicillin but for the future development of antibiotic therapy. Of other antibiotics that are being used in some volume now, tyrothricin seems to have an extremely low sensitizing capacity. Grolnick<sup>33</sup> reports that tyrothricin is a poor sensitizing agent. The reviewers who have by now had wide experience with the clinical topical use of tyrothricin have never seen a case of allergic sensitization from it. Because of its low sensitizing capacity and its unfitness for systemic use, tyrothricin is the antibiotic of choice for local application in cutaneous infections with micro-organisms which are susceptible to it. Unfortunately, the same does not apply to streptomycin. This agent is not yet extensively employed because it is still very expensive and but recently released from rationed control. M. Strauss<sup>77</sup> and Warring have collected a series of cases of eczematous dermatitis from streptomycin in nurses handling the drug and one of us (M. L.) has observed a case of eczematous sensitization from its topical use (1:500 aq. sol) in otitis externa (presumably a *pseudomonas aeruginosa* infection where it has been reported<sup>14</sup> to be curative). Reuse upon recurrence two months after original topical exhibition resulted in exacerbation of the eczema. Patch test with a solution corresponding in potency to that originally used gave a 4+ eczematous reaction.

This brings up the whole problem of the eczematous forms of the superficial mycoses; it has been observed before<sup>79</sup> that these could be looked upon as allergic eczematous contact-type dermatitis and in principle no different from the condition caused by, say, poison ivy, nail polish or any other eczematogenic allergen. Both dermatophytosis and dermatophytids are eczematous sensitizations to fungi and/or their products. The clinical and histologic appearances of the superficial mycoses,

the affinity of dermatophytes for dead material such as keratin, their lodgement and proliferation in the stratum corneum where they and their products act virtually like a continuous patch test, the similarity to penicillin reactions that are eczematous and which are associated with positive eczematous reactions to patch tests with penicillin—all these points again tend to support the close resemblance of eczematous fungous infections and “ids” and of allergic eczematous contact-type dermatitis. There is some evidence also to indicate a common eczematogenic allergen present in some common dermatotropic fungi and in penicillin.

Cormia and Lewis<sup>19</sup> and Cormia, Lewis and Hopper<sup>20</sup> have studied penicillin sensitization experimentally with special reference to cross-sensitization with trichophytin. Positive evidence of such cross-sensitization was obtained by tuberculin-type reactions and by the Schultz-Dale experiment to both penicillin and trichophytin, no matter which was used as the original.

Peck and Siegal<sup>65</sup> reported a successful hyposensitization to penicillin in a patient who had developed an erythematous-vesicular eruption from the drug. The patient's hypersensitivity was also manifested by a forty-eight-hour delayed tuberculin-type response to intracutaneous test with penicillin. As there is evidence that spontaneous hyposensitization or desensitization occurs in the eczematous and urticarial forms of allergic penicillin hypersensitivity, the possibility cannot be ruled out that the desensitization in the case described by Peck and Siegal may have occurred spontaneously.

#### MISCELLANY

Sulzberger and Baer<sup>80</sup> and Blum, Baer and Sulzberger<sup>11</sup> studied a case of hypersensitivity to light which manifested itself by urticaria and systemic reactions and showed the presence of Prausnitz-Küstner reagins. This finding, together with a limited effective range of ultra violet radiation ( $\lambda < 3700$ ), permits speculation on the effect of the radiation on tissue (containing proantigen?) resulting in conversion of the proantigen into antigen or in the release of the antigen and thus the evocation of the specific reaction.

In another study the same workers<sup>4</sup> illustrate the effect of Pyribenzamine on dermographism. With a simple technique of standardizing the dermographic stroke by using equal strips of adhesive tape that were ripped off before and after the exhibition of Pyribenzamine, the inhibiting effect on whealing was demonstrated in a convincing manner. No conclusion about the role of histamine is drawn from the experiment.

The interest in atabrine dermatitis seems to have reached its peak. Extensive clinical descriptions and statistical analyses have appeared.<sup>1,6,8,9,34,90</sup> The exact mechanism of the eruption remains, however, obscure. Not even some of the marks of allergy that commonly obtain for some of the other drug eruptions can always be shown in atabrine dermatitis. The study of these atabrine dermatoses is particularly difficult because exacerbation upon readministration is often lacking. This does not, however, deny an allergic mechanism. It is so easy to imagine prolonged sojourn of the drug *in vivo*, strange hapten conjugation, autosensitization, et cetera, to explain the odd course of this dermatosis.

A revival of interest and speculation about the allergic nature of infectious processes, particularly syphilis, is evident by the appearance of two long papers on the subject. Leider<sup>50</sup> wrote a synthetic account of his conception of the clinical and immunologic events of syphilis against a map of allergic concepts such as are detailed in this review. Urbach and Beerman<sup>87</sup> wrote another account. Perusal of both these papers are recommended as an intellectual exercise and for further speculation and study. The points of difference may briefly be spotted here by quoting from Urbach and Beerman as follows: “Allergy may be defined as the alteration in an organism's capacity to react to a *non-toxic* (our italics) substance

as the result of the production of antibodies. Allergy can therefore express itself either as hypersensitiveness or as hyposensitiveness. Immunity is a state of increased resistance to, or tolerance of, *pathogenic*† agents and/or their products, the change being due to an increase in specific antibodies. Thus according to these definitions, immunity is a special form of allergic hypersensitiveness. In other words, the concept of allergy is more comprehensive; the two terms must not, therefore, be set against each other." While one can agree in a general way with the subcategorization of some forms of immunity under allergy, there is a lack of clarity in the manner the terms "nontoxic," "pathogenic," "hypersensitiveness," "hyposensitiveness," "resistance" and "tolerance" are used.

In consequence of such theoretical points as are discussed in these papers, we noted reports of work by Arnold, Mahoney and Cutler<sup>2,3</sup> on problems of reinfectivity with syphilis in animals after apparent clinical cure with penicillin. Such data will be of the utmost practical and theoretical interest.

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†Our italics.—EDITOR.

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## ANTI-ASTHMATIC EFFECTS OF A NEW SYNTHETIC ANTISPASMODIC

(Continued from Page 540)

vertigo or dizziness in a minority of cases; this is minimized or abolished by proper dosage control.

The following objective criteria for the relief of asthma were employed: disappearance or marked diminution of rhonchi; relief of dyspnea with shortening of the phase of expiration; increase in vital capacity. Subjective criteria were: diminution or disappearance of wheezing, shortness of breath and coughing; ability to sleep horizontally after previous orthopnea; enjoyment of nights of rest after previously consistently disturbed nights. Eighty per cent of moderately severe but still ambulatory asthmatic patients benefited from the use of the drug. During these investigations a definite effort was made to exclude that 25 per cent of asthmatic patients who admit or claim temporary benefit of some degree from any medication, however inert.

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450 Sutter Street,  
San Francisco, California.

# News Items

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## FOURTH ANNUAL MEETING OF THE AMERICAN COLLEGE OF ALLERGISTS

Hotel Pennsylvania, New York City

March 12, 13 and 14, 1948

*(Important Notice. All Members Please Read Carefully)*

This session promises to be an outstanding success. Both members and non-members are urged to attend. All members and other allergists on our mailing list will be receiving a room reservation card for the Hotel Pennsylvania early in January. If anyone is missed, please write to the Secretary-Treasurer, 423 LaSalle Medical Building, Minneapolis 2, Minnesota, for your card. Fill in these cards and mail them immediately, as all reservations must be made directly with the hotel by those attending the meeting.

Both members and non-members are required to register and receive a badge. The registration desk will open Thursday afternoon, March 11, at 2:00 P.M. Fellows and Associate Fellows must present their membership cards at the desk. There will be no charge for registration.

A meeting of the Board of Directors will be held Thursday morning, March 11, from 9:00 to 10:00, and a meeting of the members of the Board of Regents and ex-officio members only will follow from 10:00 to 12:00. At 2:00 P.M. Thursday, the various committees will meet; namely, the Standardization Committee in conjunction with the Sub-Committee for Certification of Allergenic Extract, New and Unused Therapeutics Committee, and the Committee on the Extension of Postgraduate Education in conjunction with the Sub-Committee on Publications. There will be a meeting of the American Society for the Certification of Allergists on Friday evening at 7:30.

Morning scientific sessions will begin at 9:00 and extend until 1:00 P.M. The afternoon sessions will be held from 2:00 to 5:30. On Saturday afternoon the program will be conducted from 2:00 to 4:00 P. M., and will be followed by the business meeting for all members at 4:15. The cocktail hour, beginning at 6:30, immediately precedes the annual informal banquet in the Georgian Room.

At the time this news item was sent to press, the Program Committee announced a symposium on three topics, focusing upon certain important aspects of allergy. Controversial subjects about which a good deal is known are usually presented. They are: (1) Mold Allergy; (2) Rhinolaryngological Allergy; and (3) Neuro-Allergy.

It is of special importance to note that the third topic, Neuro-Allergy, will be the subject of intensive research during the coming year. It is with a good deal of pleasure, therefore, that the College announces specific plans for the presentation of scientific developments along this line.

The Program Committee urges all Fellows and Associate Fellows who plan to submit papers for consideration to do so before February 1, so that they may be published in the program booklet which will be mailed about ten days before the annual session. All papers should be sent in duplicate, 250 words in length abstracted. Papers may also be presented *by title*. There is no limit to the papers *by title* which anyone can submit and be assured of their publication in the ANNALS, if accepted. However, only one paper of this type from each author may be presented at the meeting. All papers presented *by title* will appear as part of the regular program,

thus assuring the author priority. Abstracts of the papers presented *by title* will be published in the ANNALS, with the papers which are actually given at the meeting. Presenting a paper *by title* does not obligate the author to attend the meeting.

It is too early to present the completed program. However, some of the topics which will be presented are as follows:

- "Transmission of Nervous Impulse"—OTTO LOEWI, M.D.
- "Clinical Significance of Acetylcholine"—JOSEPH G. HOPKINS, M.D.
- "A New Antihistaminic Compound for the Treatment of Urticaria and Hay Fever"—SALVATORE N. SALETTA, M.D.
- "Aerosol Penicillin in Allergic Patients with Respiratory Infections"—MAYER A. GREEN, M.D.
- "A Durhan Type of Pollen-Collecting Chamber for Sixty-seven Cents"—BERNARD DICKSTEIN, M.D.
- "Vulva Pruritus Associated with Hay Fever"—WILLIAM F. MITCHELL, M.D.
- "Correlation of Experimental Data with Clinical Behavior of a Group of Synthetic Antihistamine Drugs"—ALEX S. FRIEDLAENDER, M.D., and SIDNEY FRIEDLAENDER, M.D.
- "Histamine-Sympathin Balance"—FRANCISCO J. FARRERONS, M.D.
- "Behavior of the Normal Histamine of the Rabbit toward Antihistaminic Substances"—FRANCISCO J. FARRERONS, M.D.
- "Chronic Urticaria—An Etiological Survey of 125 Cases"—GEORGE L. WALDBOTT, M.D., and GEORGE L. SPRINKLE, M.D.
- "The Rh Factor in Immunological Reactions"—ALEXANDER S. WIENER, M.D.
- "A Clinical Evaluation of a New Antihistaminic Drug Antistine"—MORRIS KAPLAN, M.D., and NORMAN J. EHRLICH, M.D.
- "Anaphylactic Shock in Mice"—PHILIP D. McMASTER, M.D.
- "Bacteriologic Studies in Multiple Sclerosis"—EDWARD C. ROSENOW, M.D., and BAYARD T. HORTON, M.D.
- "Retrobulbar Neuritis: Treatment with Histamine"—HENRY P. WAGENER, M.D., and BAYARD T. HORTON, M.D.
- "Neurological Allergies and Histamine"—HINTON D. JONEZ, M.D.
- "Immediate Urticarial Reactions to Intradermal Injections of Bacterial Antigens"—BENNETT KRAFT, M.D., MARK H. MOTHERSILL, M.D., and R. H. NESTMANN, M.D.
- "The Electroencephalogram of Allergic Children"—SUSAN C. DEES, M.D., and HANS LOWENBACH, M.D.
- "Antitoxin Studies on Refined Tetanus and Diphtheria Toxoids in Allergic Children"—H. G. RAPAPORT, M.D., and M. MURRAY PESHKIN, M.D.
- "Comparison of the Antihistaminic Action of Pyribenzamine and Epinephrine in the Human Skin"—H. A. ABRAMSON, M.D., and S. GROSBERG, M.D.
- "Clinical Evaluation of a New Antihistamine Drug; 2-Dimethylaminoethoxy-Phenyl-Methyl-2-Picoline Succinate (Decapryn)"—ETHAN ALLAN BROWN, M.D.
- "Studies on Acute Disseminated Encephalomyelitis in Rhesus Monkeys"—ELVIN A. KABAT, M.D., ABNER WOLF, M.D., and ADA E. BEZER, M.D.

#### POST CONVENTION PLEASURE TRIP

An official trip to Bermuda has been arranged for any of those attending the Fourth Annual Session of the American College of Allergists at the Hotel Pennsylvania, New York City, March 12-14, 1948. Arrangements have been made with the Travel Shop, 105 South Fifth Street, Minneapolis, to handle all details, without charge, at official transportation and hotel rates. Plans are being made for leaving New York on Monday morning, March 15, by a mammoth, luxurious Pan American Clipper and arriving in sunny Bermuda just three hours later. The round-trip air fare, New York to Bermuda, is \$144.90, U. S. tax included. First class hotel accommodations will be provided in Bermuda at rates ranging from \$12 per day with meals.



## NEWS ITEMS

When making reservations for this official post-convention trip, please state the names in full of those in your party desiring to go, together with their age, sex, nationality, and the number of days your party desires to stay in Bermuda. A deposit of \$100 for each person making reservations should be enclosed. Do not miss this opportunity by delaying! Limited plane space and hotel accommodations make early reservations necessary.

### CINCINNATI INSTRUCTIONAL COURSE

One of the largest and most successful instructional courses in allergy ever to be held was recently conducted by the College under the auspices of the College of Medicine, University of Cincinnati, November 3-8, inclusive. There were forty-three instructors, the majority from the teaching staffs of leading universities in the United States. The total registration of physicians attending this course, exclusive of the faculty, was 169. Dr. George E. Rockwell was chairman and director of the committee.

### THE AMERICAN ASSOCIATION OF IMMUNOLOGISTS

The thirty-second annual meeting of the American Association of Immunologists will be held with the Federation of American Societies for Experimental Biology in Atlantic City, March 15 and 16, 1948. The date of the usual joint meeting with the American Society for Experimental Pathology will probably be March 16.

The Federation headquarters will be at the Chalfonte-Haddon Hall.

### SOUTHWEST ALLERGY FORUM

We are pleased to announce that the next meeting of the Southwest Allergy Forum will be held on April 5 and 6, 1948, at the Biltmore Hotel, Oklahoma City, Oklahoma. The Executive Committee of this Society is composed of: Dr. Herbert J. Rinkel, president, Kansas City, Mo.; Dr. Sim Hulsey, president-elect, Fort Worth, Texas; Dr. Fannie L. Leney, secretary-treasurer, Oklahoma City, Okla.; Dr. Carrol Pounders, Oklahoma City, Okla.; Dr. Nesbeitt Miller, Oklahoma City, Oklahoma.

### CENTRAL PENNSYLVANIA ALLERGY SOCIETY

The recent meeting of the Central Pennsylvania Allergy Society was attended by nearly one hundred and fifty members. Dr. Stephen Lockey of Lancaster, Dr. Harvey Simmons of Harrisburg, and Dr. Ralph M. Mulligan of Reading, were re-elected to the offices of president, vice president, and secretary-treasurer, respectively, for the year 1948. The next meeting will be held in York, in April, 1948, with Dr. Arthur Kalisch as chairman of arrangements.

The following men were elected to membership: Dr. Walter Werley, Reading; Dr. Paul Craig, Reading; Dr. Archibald Judd, Hamburg; Dr. Z. Estes, Lancaster; Dr. J. Welch, Lancaster; Dr. J. D. Diehl, West Chester; Dr. Lester Lowle, Lewisburg; Dr. Nelson Scharadin, Cleona; Dr. B. H. Hamner, Williamsport; Dr. Harry Mullin, Scranton; Dr. Luther King, Meadville; Dr. Wilfred Langley, Sayre; Dr. Charles Koniver, Allentown.

\* \* \*

Harry L. Rogers, M.D., announces the removal of his office to 1537 Pine Street, Philadelphia, Pa.

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